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DATE: Wednesday, August 18, 2004

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☐	L3	(exendin$ or exendin-4 or exendin4) same (pharmaceutical same (formulation or preparation or composition)) and administer$	25
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☐	L1	(exendin$ or exendin-4 or exendin4) and (pharmaceutical same (formulation or preparation or composition))	265

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Search Results - Record(s) 1 through 30 of 30 returned.

☐ 1. Document ID: US 20040142866 A1

Using default format because multiple data bases are involved.

L2: Entry 1 of 30 File: PGPB Jul 22, 2004

PGPUB-DOCUMENT-NUMBER: 20040142866
PGPUB-FILING-TYPE: new
DOCUMENT-IDENTIFIER: US 20040142866 A1

TITLE: Derivatives of the insulinotropic peptide exendin-4 and methods of production thereof

PUBLICATION-DATE: July 22, 2004

INVENTOR-INFORMATION:

NAME	CITY	STATE	COUNTRY	RULE-47
Sun, Yukun	Shanghai		CN	
Wu, Dengxi	Shanghai		CN	
Chen, Wen	Shanghai		CN	
Zhu, Zhiyong	Shanghai		CN	

US-CL-CURRENT: 514/12; 530/350

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | Claims | KWIC | Draw Desc | Image

☐ 2. Document ID: US 20040121009 A1

L2: Entry 2 of 30 File: PGPB Jun 24, 2004

PGPUB-DOCUMENT-NUMBER: 20040121009
PGPUB-FILING-TYPE: new
DOCUMENT-IDENTIFIER: US 20040121009 A1

TITLE: Method of modifying the release profile of sustained release compositions

PUBLICATION-DATE: June 24, 2004

INVENTOR-INFORMATION:

NAME	CITY	STATE	COUNTRY	RULE-47
Dasch, James R.	Needham	MA	US	
Riley, M. Gary I.	Boston	MA	US	
Burke, Paul A.	Oxnard	CA	US	
Steitz-Abadi, Susan A.	Barrington	RI	US	
Zale, Stephen E.	Hopkinton	MA	US	

S-CL-CURRENT: 424/468; 514/179

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | Claims | KWIC | Draw Desc | Image

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☐ 3. Document ID: US 20040106547 A1

L2: Entry 3 of 30 File: PGPB Jun 3, 2004

GPUB-DOCUMENT-NUMBER: 20040106547
GPUB-FILING-TYPE: new
OCUMENT-IDENTIFIER: US 20040106547 A1

ITLE: Novel peptide agonists of GLP-1 activity

UBLICATION-DATE: June 3, 2004

NVENTOR-INFORMATION:

AME	CITY	STATE	COUNTRY	RULE-47
arsen, Bjarne Due	Bronshoj		DK	
ikkelsen, Jens Damsgaard	Lyngby		DK	
eve, Soren	Lyngby		DK	

S-CL-CURRENT: 514/12; 530/350

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | Claims | KWIC | Draw Desc | Image

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☐ 4. Document ID: US 20040092443 A1

L2: Entry 4 of 30 File: PGPB May 13, 2004

GPUB-DOCUMENT-NUMBER: 20040092443
GPUB-FILING-TYPE: new
OCUMENT-IDENTIFIER: US 20040092443 A1

ITLE: Long-acting exendins and exendin agonists

UBLICATION-DATE: May 13, 2004

NVENTOR-INFORMATION:

AME	CITY	STATE	COUNTRY	RULE-47
ridkin, Matityahu	Rehovot		IL	
hechter, Yoram	Rehovot		IL	
subery, Haim	El-Ad		IL	

S-CL-CURRENT: 514/12; 530/409

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | Claims | KWIC | Draw Desc | Image

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☐ 5. Document ID: US 20040072736 A1

L2: Entry 5 of 30 File: PGPB Apr 15, 2004

GPUB-DOCUMENT-NUMBER: 20040072736
GPUB-FILING-TYPE: new
OCUMENT-IDENTIFIER: US 20040072736 A1

ITLE: Bicyclic oligopeptides

UBLICATION-DATE: April 15, 2004

NVENTOR-INFORMATION:

AME	CITY	STATE	COUNTRY	RULE-47
otterat, Olivier	Mittelbiberach		DE	
treicher, Ruediger	Biberach		DE	
agner, Klaus	Warthausen		DE	
aurer, Till	Oberstadion		DE	
ack, Juergen	Biberach		DE	
eters, Stefan	Biberach		DE	

S-CL-CURRENT: 514/9; 530/317

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | Claims | KWIC | Draw Desc | Image

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☐ 6. Document ID: US 20040023974 A1

L2: Entry 6 of 30 File: PGPB Feb 5, 2004

GPUB-DOCUMENT-NUMBER: 20040023974
GPUB-FILING-TYPE: new
OCUMENT-IDENTIFIER: US 20040023974 A1

ITLE: Cyclic sulfamide derivatives and methods of use

UBLICATION-DATE: February 5, 2004

NVENTOR-INFORMATION:

AME	CITY	STATE	COUNTRY	RULE-47
oppola, Gary Mark	Budd Lake	NJ	US	
avies, John William	Montclair	NJ	US	
ewell, Charles Francis	Sudbury	MA	US	
i, Yu-Chin	Edison	NJ	US	
areing, James Richard	Randolph	NJ	US	
perbeck, Donald Mark	Berkeley Heights	NJ	US	
tams, Travis Matthew	Belle Mead	NJ	US	
opiol, Sidney Wolf	Fair Lawn	NJ	US	
lattas, Isidoros	Summit	NJ	US	

S-CL-CURRENT: 514/252.05; 514/341, 514/362, 544/238, 546/268.7, 548/135

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | Claims | KWIC | Draw Desc | Image

☐ 7. Document ID: US 20040023871 A1

L2: Entry 7 of 30 File: PGPB Feb 5, 2004

GPUB-DOCUMENT-NUMBER: 20040023871
GPUB-FILING-TYPE: new
OCUMENT-IDENTIFIER: US 20040023871 A1

ITLE: Use of exendins and agonists thereof for the treatment of gestational diabetes mellitus

UBLICATION-DATE: February 5, 2004

NVENTOR-INFORMATION:

NAME	CITY	STATE	COUNTRY	RULE-47
Hiles, Richard A.	San Diego	CA	US	
Prickett, Kathryn S.	San Diego	CA	US	

S-CL-CURRENT: 514/12

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | Claims | KWIC | Draw Desc | Image

☐ 8. Document ID: US 20030212104 A1

L2: Entry 8 of 30 File: PGPB Nov 13, 2003

GPUB-DOCUMENT-NUMBER: 20030212104
GPUB-FILING-TYPE: new
OCUMENT-IDENTIFIER: US 20030212104 A1

ITLE: Treatment of diabetes and diabetic complications with NHE-1 inhibitors

UBLICATION-DATE: November 13, 2003

NVENTOR-INFORMATION:

NAME	CITY	STATE	COUNTRY	RULE-47
Tracey, W. Ross	Niantic	CT	US	
Treadway, Judith L.	Mystic	CT	US	

S-CL-CURRENT: 514/314; 514/12, 514/171, 514/3, 514/342, 514/369, 514/406, 514/592, 514/635

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | Claims | KWIC | Draw Desc | Image

☐ 9. Document ID: US 20030087821 A1

L2: Entry 9 of 30 File: PGPB May 8, 2003

PGPUB-DOCUMENT-NUMBER: 20030087821
PGPUB-FILING-TYPE: new
DOCUMENT-IDENTIFIER: US 20030087821 A1

TITLE: Exendins, exendin agonists, and methods for their use

PUBLICATION-DATE: May 8, 2003

INVENTOR-INFORMATION:

NAME	CITY	STATE	COUNTRY	RULE-47
Beeley, Nigel Robert Arnold	Solana Beach	CA	US	
Prickett, Kathryn S.	San Diego	CA	US	
Bhavsar, Sunil	San Diego	CA	US	

US-CL-CURRENT: 514/12

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | Claims | KWIC | Draw Desc | Image

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☐ 10. Document ID: US 20030087820 A1

L2: Entry 10 of 30 File: PGPB May 8, 2003

PGPUB-DOCUMENT-NUMBER: 20030087820
PGPUB-FILING-TYPE: new
DOCUMENT-IDENTIFIER: US 20030087820 A1

TITLE: Novel exendin agonist formulations and methods of administration thereof

PUBLICATION-DATE: May 8, 2003

INVENTOR-INFORMATION:

NAME	CITY	STATE	COUNTRY	RULE-47
Young, Andrew A.	La Jolla	CA	US	
Kolterman, Orville G.	Poway	CA	US	

US-CL-CURRENT: 514/12

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | Claims | KWIC | Draw Desc | Image

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☐ 11. Document ID: US 20030073729 A1

L2: Entry 11 of 30 File: PGPB Apr 17, 2003

GPUB-DOCUMENT-NUMBER: 20030073729
GPUB-FILING-TYPE: new
OCUMENT-IDENTIFIER: US 20030073729 A1

ITLE: Medicaments for diabetic complication and neuropathy, and uses thereof

UBLICATION-DATE: April 17, 2003

INVENTOR-INFORMATION:

NAME	CITY	STATE	COUNTRY	RULE-47
Kitahara, Yoshiro	Kawasaki-shi		JP	
Miura, Kyoko	Kawasaki-shi		JP	

US-CL-CURRENT: 514/369

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | Claims | KWIC | Draw Desc | Image

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☐ 12. Document ID: US 20030073728 A1

L2: Entry 12 of 30 File: PGPB Apr 17, 2003

PGPUB-DOCUMENT-NUMBER: 20030073728
PGPUB-FILING-TYPE: new
DOCUMENT-IDENTIFIER: US 20030073728 A1

TITLE: Combination of FBPase inhibitors and antidiabetic agents useful for the treatment of diabetes

PUBLICATION-DATE: April 17, 2003

INVENTOR-INFORMATION:

NAME	CITY	STATE	COUNTRY	RULE-47
van Poelje, Paul D.	La Jolla	CA	US	
Erion, Mark D.	Del Mar	CA	US	
Fujiwara, Toshihiko			US	

US-CL-CURRENT: 514/369; 514/592

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | Claims | KWIC | Draw Desc | Image

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☐ 13. Document ID: US 20030036504 A1

L2: Entry 13 of 30 File: PGPB Feb 20, 2003

GPUB-DOCUMENT-NUMBER: 20030036504
GPUB-FILING-TYPE: new
OCUMENT-IDENTIFIER: US 20030036504 A1

ITLE: Use of exendins and agonists thereof for modulation of triglyceride levels and treatment f dyslipidemia

UBLICATION-DATE: February 20, 2003

NVENTOR-INFORMATION:

NAME	CITY	STATE	COUNTRY	RULE-47
Kolterman, Orville G.	Poway	CA	US	
Young, Andrew A.	Point Loma	CA	US	

US-CL-CURRENT: 514/12

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | Claims | KWIC | Draw Desc | Image

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☐ 14. Document ID: US 20020141985 A1

L2: Entry 14 of 30 File: PGPB Oct 3, 2002

PGPUB-DOCUMENT-NUMBER: 20020141985
PGPUB-FILING-TYPE: new
DOCUMENT-IDENTIFIER: US 20020141985 A1

TITLE: Peptide YY and peptide YY agonists for treatment of metabolic disorders

PUBLICATION-DATE: October 3, 2002

INVENTOR-INFORMATION:

NAME	CITY	STATE	COUNTRY	RULE-47
Pittner, Richard A.	San Diego	CA	US	
Young, Andrew A.	La Jolla	CA	US	
Paterniti, James R. JR.	San Diego	CA	US	

US-CL-CURRENT: 424/94.1

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | Claims | KWIC | Draw Desc | Image

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☐ 15. Document ID: US 20020137666 A1

L2: Entry 15 of 30 File: PGPB Sep 26, 2002

PGPUB-DOCUMENT-NUMBER: 20020137666
PGPUB-FILING-TYPE: new
DOCUMENT-IDENTIFIER: US 20020137666 A1

TITLE: USE OF EXENDINS AND AGONISTS THEREOF FOR THE REDUCTION OF FOOD INTAKE

PUBLICATION-DATE: September 26, 2002

INVENTOR-INFORMATION:

NAME	CITY	STATE	COUNTRY	RULE-47
BEELEY, NIGEL ROBERT ARNOLD	SOLANA BEACH	CA	US	
PRICKETT, KATHRYN S.	SAN DIEGO	CA	US	
BHAVSAR, SUNIL	SAN DIEGO	CA	US	

US-CL-CURRENT: 514/2; 514/12, 530/350

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | Claims | KWIC | Draw Desc | Image

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☐ 16. Document ID: US 20010047084 A1

L2: Entry 16 of 30 File: PGPB Nov 29, 2001

PGPUB-DOCUMENT-NUMBER: 20010047084
PGPUB-FILING-TYPE: new
DOCUMENT-IDENTIFIER: US 20010047084 A1

TITLE: Extendin derivatives

PUBLICATION-DATE: November 29, 2001

INVENTOR-INFORMATION:

NAME	CITY	STATE	COUNTRY	RULE-47
Knudsen, Liselotte Bjerre	Valby		DK	
Huusfeldt, Per Olaf	Copenhagen K		DK	
Nielsen, Per Franklin	Vaerlose		DK	
Madsen, Kjeld	Vaerlose		DK	

US-CL-CURRENT: 530/399

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | Claims | KWMC | Draw Desc | Image

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☐ 17. Document ID: US 6767887 B1

L2: Entry 17 of 30 File: USPT Jul 27, 2004

US-PAT-NO: 6767887
DOCUMENT-IDENTIFIER: US 6767887 B1

TITLE: Exendin analogues, processes for their preparation and medicaments containing them

DATE-ISSUED: July 27, 2004

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Hoffmann; Eike	Viernheim			DE
Goke; Rudiger	Marburg			DE
Goke; Burkhard-Johannes	Marburg			DE

US-CL-CURRENT: 514/2; 514/866, 530/324

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | Claims | KWMC | Draw Desc | Image

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☐ 18. Document ID: US 6703359 B1

L2: Entry 18 of 30 File: USPT Mar 9, 2004

US-PAT-NO: 6703359
DOCUMENT-IDENTIFIER: US 6703359 B1

TITLE: Inotropic and diuretic effects of exendin and GLP-1

DATE-ISSUED: March 9, 2004

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Young; Andrew A.	San Diego	CA		
Vine; Will	Poway	CA		
Beeley; Nigel R. A.	Solana Beach	CA		
Prickett; Kathryn	San Diego	CA		

US-CL-CURRENT: 514/2; 514/866, 530/324

Full | Title | Citation | Front | Review | Classification | Date | Reference | [illegible] | [illegible] | Claims | KWIC | Draw Desc | Image

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☐ 19. Document ID: US 6602694 B1

L2: Entry 19 of 30 File: USPT Aug 5, 2003

US-PAT-NO: 6602694
DOCUMENT-IDENTIFIER: US 6602694 B1

TITLE: Uncoupling protein 4 (UCP-4)

DATE-ISSUED: August 5, 2003

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Albrandt; Keith	San Diego	CA		
Beaumont; Kevin	San Diego	CA		
Young; Andrew A.	San Diego	CA		

US-CL-CURRENT: 435/183; 530/333, 530/350

Full | Title | Citation | Front | Review | Classification | Date | Reference | [illegible] | [illegible] | Claims | KWIC | Draw Desc | Image

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☐ 20. Document ID: US 6528486 B1

L2: Entry 20 of 30 File: USPT Mar 4, 2003

US-PAT-NO: 6528486
DOCUMENT-IDENTIFIER: US 6528486 B1

TITLE: Peptide agonists of GLP-1 activity

DATE-ISSUED: March 4, 2003

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Larsen; Bjarne Due	Br.o slashed.nsh.o slashed.j			DK

Mikkelsen; Jens Damsgaard	Lyngby	DK
Neve; S.o slashed.ren	Lyngby	DK

US-CL-CURRENT: 514/12; 514/2, 530/300, 530/303

Full | Title | Citation | Front | Review | Classification | Date | Reference | Claims | KWIC | Draw Desc | Image

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☐ 21. Document ID: US 6506724 B1

L2: Entry 21 of 30 File: USPT Jan 14, 2003

US-PAT-NO: 6506724
DOCUMENT-IDENTIFIER: US 6506724 B1

TITLE: Use of exendins and agonists thereof for the treatment of gestational diabetes mellitus

DATE-ISSUED: January 14, 2003

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Hiles; Richard A.	San Diego	CA		
Prickett; Kathryn S.	San Diego	CA		

US-CL-CURRENT: 514/2; 514/12, 514/3, 514/4, 514/866, 530/300, 530/324, 530/325

Full | Title | Citation | Front | Review | Classification | Date | Reference | Claims | KWIC | Draw Desc | Image

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☐ 22. Document ID: US 5424286 A

L2: Entry 22 of 30 File: USPT Jun 13, 1995

US-PAT-NO: 5424286
DOCUMENT-IDENTIFIER: US 5424286 A

TITLE: Exendin-3 and exendin-4 polypeptides, and pharmaceutical compositions comprising same

DATE-ISSUED: June 13, 1995

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Eng; John	Bronx	NY	10471	

US-CL-CURRENT: 514/2; 435/69.1, 514/866, 530/324

Full | Title | Citation | Front | Review | Classification | Date | Reference | Claims | KWIC | Draw Desc | Image

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☐ 23. Document ID: DE 19921537 A1

L2: Entry 23 of 30 File: EPAB Nov 23, 2000

3-NO: DE019921537A1
CUMENT-IDENTIFIER: DE 19921537 A1
TLE: Treating carbohydrate metabolism disorders, especially diabetes, comprises activating ulin-secreting b-cells using glucagon-related peptide, glucose-dependent insulinotropic ypeptide, exendin-4 or related drugs

3N-DATE: November 23, 2000

VENTOR-INFORMATION:

ME	COUNTRY
ERSCH, DIETER	DE

T-CL (IPC): A61 K 38/22; A61 K 38/26
R-CL (EPC): A61K038/26

Full | Title | Citation | Front | Review | Classification | Date | Reference | Claims | KWIC | Draw Desc | Image

☐ 24. Document ID: WO 9940788 A1

L2: Entry 24 of 30 File: EPAB Aug 19, 1999

3-NO: WO009940788A1
CUMENT-IDENTIFIER: WO 9940788 A1
TLE: INOTROPIC AND DIURETIC EFFECTS OF EXENDIN AND GLP-1

3N-DATE: August 19, 1999

VENTOR-INFORMATION:

ME	COUNTRY
UNG, ANDREW A	US
NE, WILL	US
ELEY, NIGEL R A	US
ICKETT, KATHRYN	US

T-CL (IPC): A01 N 37/18
R-CL (EPC): A61K031/00

Full | Title | Citation | Front | Review | Classification | Date | Reference | Claims | KWIC | Draw Desc | Image

☐ 25. Document ID: WO 9830231 A1

L2: Entry 25 of 30 File: EPAB Jul 16, 1998

3-NO: WO009830231A1
CUMENT-IDENTIFIER: WO 9830231 A1
TLE: USE OF EXENDINS AND AGONISTS THEREOF FOR THE REDUCTION OF FOOD INTAKE

3N-DATE: July 16, 1998

VENTOR-INFORMATION:

ME	COUNTRY

EELEY, NIGEL ROBERT ARNOLD
RICKETT, KATHRYN S
HAVSAR, SUNIL

NT-CL (IPC): A61 K 38/16
NR-CL (EPC): C07K014/575

Full | Title | Citation | Front | Review | Classification | Date | Reference | Claims | KWIC | Draw Desc | Image

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☐ 26. Document ID: WO 2004050115 A2

L2: Entry 26 of 30 File: DWPI Jun 17, 2004

RWENT-ACC-NO: 2004-480530
RWENT-WEEK: 200445
OPYRIGHT 2004 DERWENT INFORMATION LTD
TLE: Treating or preventing diabetes or diabetes-related disease by administering exendin-4 ompound and thiazolidinedione insulin sensitizer to patient

NVENTOR: KNUDSEN, L B

RIORITY-DATA: 2002US-431999P (December 9, 2002), 2002DK-0001864 (December 3, 2002)

ATENT-FAMILY:

UB-NO	PUB-DATE	LANGUAGE	PAGES	MAIN-IPC
O 2004050115 A2	June 17, 2004	E	031	A61K038/22

NT-CL (IPC): A61 K 31/426; A61 K 31/427; A61 K 38/22; A61 P 3/10

Full | Title | Citation | Front | Review | Classification | Date | Reference | Claims | KWIC | Draw Desc | Image

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☐ 27. Document ID: WO 2004010992 A1

L2: Entry 27 of 30 File: DWPI Feb 5, 2004

RWENT-ACC-NO: 2004-203485
RWENT-WEEK: 200419
PYRIGHT 2004 DERWENT INFORMATION LTD
TLE: New chromane and chromene compounds are peroxisome proliferator activated receptor alpha onist, useful for treating e.g. hyperlipidemia, obesity and atherosclerosis

NVENTOR: DESAI, R C; SAHOO, S

IORITY-DATA: 2002US-399518P (July 30, 2002)

TENT-FAMILY:

UB-NO	PUB-DATE	LANGUAGE	PAGES	MAIN-IPC
O 2004010992 A1	February 5, 2004	E	057	A61K031/352

T-CL (IPC): A61 K 31/352; C07 D 311/04

☐ 28. Document ID: AU 2003239910 A1, WO 2003099314 A1

L2: Entry 28 of 30 File: DWPI Dec 12, 2003

DERWENT-ACC-NO: 2004-042706
DERWENT-WEEK: 200443

TITLE: Pharmaceutical composition for treating diabetes, impaired glucose tolerance, obesity, dyslipidemia or cardiovascular disease comprises an exendin or an exendin agonist peptide in an extended-release formulation

INVENTOR: KOLTERMAN, O G; YOUNG, A A

PRIORITY-DATA: 2002US-0157224 (May 28, 2002)

PATENT-FAMILY:

PUB-NO	PUB-DATE	LANGUAGE	PAGES	MAIN-IPC
AU 2003239910 A1	December 12, 2003		000	A61K038/00
WO 2003099314 A1	December 4, 2003	E	173	A61K038/00

INT-CL (IPC): A61 K 38/00; A61 K 38/16; A61 K 45/00; C07 K 7/00

☐ 29. Document ID: DE 19921537 A1

L2: Entry 29 of 30 File: DWPI Nov 23, 2000

DERWENT-ACC-NO: 2001-050874
DERWENT-WEEK: 200107

TITLE: Treating carbohydrate metabolism disorders, especially diabetes, comprises activating insulin-secreting b-cells using glucagon-related peptide, glucose-dependent insulinotropic polypeptide, exendin-4 or related drugs

INVENTOR: HOERSCH, D

PRIORITY-DATA: 1999DE-1021537 (May 11, 1999)

PATENT-FAMILY:

PUB-NO	PUB-DATE	LANGUAGE	PAGES	MAIN-IPC
DE 19921537 A1	November 23, 2000		010	A61K038/22

INT-CL (IPC): A61 K 38/22; A61 K 38/26

☐ 30. Document ID: US 6703359 B1, WO 9940788 A1, AU 9926596 A, EP 1054594 A1, JP 2002509078 W, AU 759058 B

L2: Entry 30 of 30 File: DWPI Mar 9, 2004

DERWENT-ACC-NO: 1999-527332
DERWENT-WEEK: 200418

TITLE: Increasing urine flow by administering peptides or peptide agonists

INVENTOR: BEELEY, N R A; PRICKETT, K ; VINE, W ; YOUNG, A A

PRIORITY-DATA: 1998US-075122P (February 13, 1998), 2000US-0622105 (September 22, 2000)

PATENT-FAMILY:

PUB-NO	PUB-DATE	LANGUAGE	PAGES	MAIN-IPC
US 6703359 B1	March 9, 2004		000	A01N037/18
WO 9940788 A1	August 19, 1999	E	000	A01N037/18
AU 9926596 A	August 30, 1999		000	A01N037/18
EP 1054594 A1	November 29, 2000	E	000	A01N037/18
JP 2002509078 W	March 26, 2002		097	A61K038/00
AU 759058 B	April 3, 2003		000	A01N037/18

INT-CL (IPC): A01 N 37/18; A61 K 38/00; A61 K 45/00; A61 P 3/12; A61 P 9/12; A61 P 13/02; A61 P 15/00

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Term	Documents
EXENDIN-4	232
EXENDIN-4S	0
EXENDIN4	13
EXENDIN4S	0
PHARMACEUTICAL	285037
PHARMACEUTICALS	83327
FORMULATION	262612
FORMULATIONS	204877
PREPARATION	1214405
PREPN	292297
((EXENDIN$ OR EXENDIN-4 OR EXENDIN4) SAME(PHARMACEUTICAL SAME (FORMULATION OR PREPARATION OR COMPOSITION))).PGPB,USPT,EPAB,DWPI,TDBD.	30

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FILE 'ADISINSIGHT' ENTERED AT 16:32:28 ON 18 AUG 2004

FILE 'ADISNEWS' ENTERED AT 16:32:28 ON 18 AUG 2004

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FILE 'DDFU' ACCESS NOT AUTHORIZED

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FILE 'DRUGB' ENTERED AT 16:32:28 ON 18 AUG 2004

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L2 0 FILE ADISINSIGHT
L3 0 FILE ADISNEWS
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L7 2 FILE CAPLUS
L8 0 FILE CEN
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TOTAL FOR ALL FILES
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L149          55 DUP REM L148 (15 DUPLICATES REMOVED)

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L149 ANSWER 1 OF 55  CAPLUS  COPYRIGHT 2004 ACS on STN DUPLICATE 1
ACCESSION NUMBER:         2004:589225  CAPLUS
TITLE:                    Derivatives of the insulinotropic peptide exendin-4
                          without internal cleavage sites
INVENTOR(S):              Sun, Yukun; Wu, Dengxi; Chen, Wen; Zhu, Zhiyong
PATENT ASSIGNEE(S):       Shanghai Huyai Bio-Lab Co., Ltd., Peop. Rep. China
SOURCE:                   U.S. Pat. Appl. Publ., 29 pp., Cont.-in-part of Appl.
                          No. PCT/CN02/00316.
                          CODEN: USXXCO
DOCUMENT TYPE:            Patent
LANGUAGE:                 English
FAMILY ACC. NUM. COUNT:   2
PATENT INFORMATION:

     PATENT NO.           KIND   DATE        APPLICATION NO.          DATE
     ---------------      ----   --------    --------------------     --------
     US 2004142866         A1    20040722    US 2003-704409           20031107
     CN 1363559            A     20020814    CN 2001-112856           20010510
     WO 2002090388         A1    20021114    WO 2002-CN316            20020508
         W:  AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CO,
             CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM,
             HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS,
             LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL,
             PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA,
             UG, US, UZ, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
         RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, CH,
             CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR,
             BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG
PRIORITY APPLN. INFO.:                       CN 2001-112856      A  20010510
                                             WO 2002-CN316       A2 20020508
AB   The present invention is directed to the development of novel exendin-4
     derivs. exhibiting advantageous glucose-regulatory properties, and to
     methods of producing these derivs., including recombinant methods in which
     these derivs. are produced by cleavage of a fusion protein containing multiple
     copies of the exendin-4 derivative peptide.  The methods of the present
     invention can be used to simplify the process of producing the disclosed
     exendin-4 derivs., thereby lowering the cost of their production

L149 ANSWER 2 OF 55  IFIPAT  COPYRIGHT 2004 IFI on STN DUPLICATE 2
AN                        10635877  IFIPAT;IFIUDB;IFICDB
TITLE:                    METHODS OF TREATING DIABETES AND OTHER BLOOD SUGAR
                          DISORDERS
INVENTOR(S):              Armentano; Donna, Belmont, MA, US
                          Gregory; Richard J., Westford, MA, US
                          Parsons; Geoffrey, Jamaica Plain, MA, US
```

Wadsworth; Samuel C., Shrewsbury, MA, US
PATENT ASSIGNEE(S): Unassigned
PATENT ASSIGNEE PROBABLE: GENZYME CORP (Probable)
AGENT: GENZYME CORPORATION;LEGAL DEPARTMENT, 15 PLEASANT ST CONNECTOR, FRAMINGHAM, MA, 01701-9322, US

	NUMBER	PK	DATE
PATENT INFORMATION:	US 2004143104	A1	20040722
APPLICATION INFORMATION:	US 2003-716326		20031117

	APPLN. NUMBER	DATE	GRANTED PATENT NO. OR STATUS
CONTINUATION-IN-PART OF:	US 2002-215272	20020807	PENDING

	NUMBER	DATE	
PRIORITY APPLN. INFO.:	US 2001-310982P	20010808	(Provisional)
FAMILY INFORMATION:	US 2004143104	20040722	

DOCUMENT TYPE: Utility
Patent Application - First Publication
FILE SEGMENT: CHEMICAL
APPLICATION

PARENT CASE DATA:

This application is a continuation in part of U.S. application Ser. No. 10/215,272 filed Aug. 7, 2002 which claims benefit of U.S. Provisional Application No. 60/310,982, filed Aug. 8, 2001. The entire teachings of the above application(s) are incorporated herein by reference.

NUMBER OF CLAIMS: 22 35 Figure(s).
DESCRIPTION OF FIGURES:

FIG. 1 shows the nucleotide (SEQ ID NO: 1) and amino acid (SEQ ID NO: 2) sequences of the signal peptide from secreted human alkaline phosphatase (SEAP) linked to Gly-8 modified human GLP1 (GLP-1-Gly8) designated SEAP.GLP-1Gly8.
FIG. 2 shows the nucleotide (SEQ ID NO: 3) and amino acid (SEQ ID NO: 4) sequences of the leader from proexendin-4 linked to GLP-1-GIy-8, designated Exendin-4.GLP-1Gly8.
FIG. 3 shows the nucleotide (SEQ ID NO: 5) and amino acid (SEQ ID NO: 6) sequences of the leader from pro-helodermin linked to GLP-1-Gly-8, designated Helodermin.GLP-1 Gly8.
FIG. 4 shows the nucleotide (SEQ ID NO: 7) and amino acid (SEQ ID NO: 8) sequences of the leader from pro-glucose dependent insulinotropic polypeptide (GIP) linked to GLP-1-Gly-8, designated GIP.GLP-IGly8.
FIG. 5 shows the nucleotide (SEQ ID NO: 9) and amino acid (SEQ ID NO: 10) sequences of the leader from pro-insulin-like growth factor 1 (IGF1) linked to GLP-1-Gly-8 via a consensus furin cleavage site, designated IGF-1 (furin).GLP-1Gly8.
FIG. 6 shows the nucleotide (SEQ ID NO: 11) and amino acid (SEQ ID NO: 12) sequences of the leader from pro-insulin-like growth factor 1 (IGF1) linked to GLP-1-Gly-8, designated IGF-1.GLP-1Gly8.
FIG. 7 shows the nucleotide (SEQ ID NO: 13) and amino acid (SEQ ID NO: 14) sequences of the leader from preproglucagon linked to GLP-1-Gly-8, designated Preproglucagon.GLP-1Gly8.
FIG. 8 shows the nucleotide (SEQ ID NO: 15) and amino acid (SEQ ID NO: 16) sequences of the leader from alpha-1 antitrypsin linked to GLP-1-Gly-8, designated Alpha-1 antitrypsin.GLP-1Gly8.
FIG. 9 shows the nucleotide (SEQ ID NO: 17) and amino acid (SEQ ID NO: 18) sequences of amino acids 1-46 of human factor IX which contains a signal peptide and a cleavage site for a prohormone convertase linked to GLP-1-Gly-8, designated Factor IX.GLP-1Gly8.
FIG. 10 shows the nucleotide (SEQ ID NO: 19) and amino acid (SEQ ID NO: 20) sequences of the leader from proexendin-4 linked to GLP-1-Gly-8 via the cleavage site of IGF-1, designated **Exendin4** (IGF-1).GLP-1Gly8.

FIG. 11 are schematics of the IGF-1.GLP-1Gly8, the Preproglucagon.GLP-1Gly8, the Alpha-1 antitrypsin.GLP-1Gly8, Exendin-4.GLP-1Gly8, the Exendin-4 (IGF-1).GLP-1Gly8, and the Factor IX.GLP-1Gly8.
FIG. 12 is a bar graph showing GLP-1 expression levels in the supernatant of 293 cells transfected with SEAP.GLP-1Gly8, Exendin-4.GLP-1 Gly8, Helodermin.GLP-1Gly8, GIP.GLP-1GLy8, IGF1(furin).GLP-1Gly8 or a control (mock).
FIG. 13 is a bar graph showing GLP-1 expression levels in the supernatant of 293 cells transfected with Alpha-1 antitrypsin. GLP-1Gly8, Preproglucagon.GLP-1Gly8, IGF-1.GLP-1Gly8, Exendin-4. GLP-1Gly8 or Exendin-4 (IGF-1).GLP-1Gly8.
FIG. 14 is a bar graph showing GLP-1 secreted from C2C12 cells transfected with Exendin-4.GLP-1Gly8, Exendin-4 (IGF-1).GLP1Gly8 or Factor IX.GLP-1Gly8.
FIG. 15 is a graph showing the plasma concentrations of GLP-1 in mice 20 transduced with GLP-1 expression plasmids by highvolume tail vein injection.
FIG. 16 is a graph showing the blood glucose levels of obese db/ db mice and their lean littermates that were treated with a high volume injection of plasmid DNA coding for **exendin4** GLP-1 under the control of the CMV enhancer/ubiquitin promoter.
FIG. 17 is a graph showing inducible expression of GLP-1 using the Valentis Gene Switch System.
FIGS. 18A-18B list examples of modified GLP-1.
FIG. 19 is a graph demonstrating that expression of GLP-1 lowers blood glucose in obese db/db mice.
FIG. 20 is a graph demonstrating that expression of GLP-1 prevents elevation of glycated hemoglobin in obese db/db mice.
FIG. 21 is a graph demonstrating that expression of GLP-1 normalizes blood glucose in obese db/db mice.
FIG. 22 is a graph demonstrating that expression of GLP-1 improves fasting blood glucose in obese db/db mice.
FIG. 23 is a graph demonstrating the insulinotropic effect of GLP-1 expression in obese db/db mice.
FIG. 24 is a graph demonstrating active plasma GLP-1 levels in obese db/db mice treated with a polynucleotide encoding for modified GLP-1.
FIG. 25 is a graph demonstrating that expression of GLP-1 reduces hyperglycemia in young obese db/db mice.
FIG. 26 is a graph demonstrating that expression of GLP-1 improves glucose tolerance test in young obese db/db mice.
FIG. 27 is a graph demonstrating that expression of GLP-1 lowers blood glucose in obese db/db mice with different starting levels of insulin.
FIG. 28 is a graph demonstrating that expression of GLP-1 improves fasting insulin levels in obese db/db mice.
FIG. 29 is a graph demonstrating that expression of GLP-1 normalizes blood glucose in fed Zucker Diabetic Fatty (ZDF) rats.
FIG. 30 is a graph demonstrating that expression of GLP-1 prevents elevation in fasting blood glucose in Zucker Diabetic Fatty (ZDF) rats.
FIG. 31 is a graph demonstrating the insulinotropic effect of GLP-1 expression in Zucker Diabetic Fatty (ZDF) rats.
FIG. 32 is a graph demonstrating active plasma GLP-1 levels in Zucker Diabetic Fatty (ZDF) rats treated with a polynucleotide encoding for modified GLP-1.
FIG. 33 is a graph demonstrating that expression of GLP-1 prevents elevation of glycated hemoglobin in Zucker Diabetic Fatty (ZDF) rats.
FIG. 34 is a graph demonstrating that expression of GLP-1 decreases food intake in Zucker Diabetic Fatty (ZDF) rats.
FIG. 35 is a graph demonstrating the effects of GLP-1 expression on body weight in Zucker Diabetic Fatty (ZDF) rats.

AB Compositions, expression vectors and host cells comprising nucleic acid which encodes a precursor glucagon-like peptide 1 (GLP-1) comprising mammalian GLP-1 linked to a heterologous signal sequence are encompassed by the present invention. The invention also relates to a method of promoting insulin production in an individual comprising administering to the individual an effective amount of a nucleic acid encoding a precursor GLP-1. The present invention also relates to a method of treating an individual having a blood sugar defect (e.g., type I or type II diabetes), comprising administering to the individual an effective amount of a nucleic acid encoding the precursor GLP-1. In a particular embodiment, the invention pertains to a method of treating an individual having a blood sugar defect comprising administering to the individual an

effective amount of a nucleic acid encoding a precursor GLP-1 wherein the precursor GLP-1 comprises a signal sequence which codes for precursor cleavage at the activation cleavage site of the precursor GLP-1.

CLMN 22 35 Figure(s).

FIG. 1 shows the nucleotide (SEQ ID NO: 1) and amino acid (SEQ ID NO: 2) sequences of the signal peptide from secreted human alkaline phosphatase (SEAP) linked to Gly-8 modified human GLP1 (GLP-1-Gly8) designated SEAP.GLP-1Gly8.

FIG. 2 shows the nucleotide (SEQ ID NO: 3) and amino acid (SEQ ID NO: 4) sequences of the leader from proexendin-4 linked to GLP-1-GIy-8, designated Exendin-4.GLP-1Gly8.

FIG. 3 shows the nucleotide (SEQ ID NO: 5) and amino acid (SEQ ID NO: 6) sequences of the leader from pro-helodermin linked to GLP-1-Gly-8, designated Helodermin.GLP-1 Gly8.

FIG. 4 shows the nucleotide (SEQ ID NO: 7) and amino acid (SEQ ID NO: 8) sequences of the leader from pro-glucose dependent insulinotropic polypeptide (GIP) linked to GLP-1-Gly-8, designated GIP.GLP-IGly8.

FIG. 5 shows the nucleotide (SEQ ID NO: 9) and amino acid (SEQ ID NO: 10) sequences of the leader from pro-insulin-like growth factor 1 (IGF1) linked to GLP-1-Gly-8 via a consensus furin cleavage site, designated IGF-1 (furin).GLP-1Gly8.

FIG. 6 shows the nucleotide (SEQ ID NO: 11) and amino acid (SEQ ID NO: 12) sequences of the leader from pro-insulin-like growth factor 1 (IGF1) linked to GLP-1-Gly-8, designated IGF-1.GLP-1Gly8.

FIG. 7 shows the nucleotide (SEQ ID NO: 13) and amino acid (SEQ ID NO: 14) sequences of the leader from preproglucagon linked to GLP-1-Gly-8, designated Preproglucagon.GLP-1Gly8.

FIG. 8 shows the nucleotide (SEQ ID NO: 15) and amino acid (SEQ ID NO: 16) sequences of the leader from alpha-1 antitrypsin linked to GLP-1-Gly-8, designated Alpha-1 antitrypsin.GLP-1Gly8.

FIG. 9 shows the nucleotide (SEQ ID NO: 17) and amino acid (SEQ ID NO: 18) sequences of amino acids 1-46 of human factor IX which contains a signal peptide and a cleavage site for a prohormone convertase linked to GLP-1-Gly-8, designated Factor IX.GLP-1Gly8.

FIG. 10 shows the nucleotide (SEQ ID NO: 19) and amino acid (SEQ ID NO: 20) sequences of the leader from proexendin-4 linked to GLP-1-Gly-8 via the cleavage site of IGF-1, designated **Exendin4** (IGF-1).GLP-1Gly8.

FIG. 11 are schematics of the IGF-1.GLP-1Gly8, the Preproglucagon.GLP-1Gly8, the Alpha-1 antitrypsin.GLP-1Gly8, Exendin-4.GLP-1Gly8, the Exendin-4 (IGF-1).GLP-1Gly8, and the Factor IX.GLP-1Gly8.

FIG. 12 is a bar graph showing GLP-1 expression levels in the supernatant of 293 cells transfected with SEAP.GLP-1Gly8, Exendin-4.GLP-1 Gly8, Helodermin.GLP-1Gly8, GIP.GLP-1GLy8, IGF1(furin).GLP-1Gly8 or a control (mock).

FIG. 13 is a bar graph showing GLP-1 expression levels in the supernatant of 293 cells transfected with Alpha-1 antitrypsin. GLP-1Gly8, Preproglucagon.GLP-1Gly8, IGF-1.GLP-1Gly8, Exendin-4. GLP-1Gly8 or Exendin-4 (IGF-1).GLP-1Gly8.

FIG. 14 is a bar graph showing GLP-1 secreted from C2C12 cells transfected with Exendin-4.GLP-1Gly8, Exendin-4 (IGF-1).GLP1Gly8 or Factor IX.GLP-1Gly8.

FIG. 15 is a graph showing the plasma concentrations of GLP-1 in mice 20 transduced with GLP-1 expression plasmids by highvolume tail vein injection.

FIG. 16 is a graph showing the blood glucose levels of obese db/ db mice and their lean littermates that were treated with a high volume injection of plasmid DNA coding for **exendin4** GLP-1 under the control of the CMV enhancer/ubiquitin promoter.

FIG. 17 is a graph showing inducible expression of GLP-1 using the Valentis Gene Switch System.

FIGS. 18A-18B list examples of modified GLP-1.

FIG. 19 is a graph demonstrating that expression of GLP-1 lowers blood glucose in obese db/db mice.

FIG. 20 is a graph demonstrating that expression of GLP-1 prevents elevation of glycated hemoglobin in obese db/db mice.

FIG. 21 is a graph demonstrating that expression of GLP-1 normalizes blood glucose in obese db/db mice.
FIG. 22 is a graph demonstrating that expression of GLP-1 improves fasting blood glucose in obese db/db mice.
FIG. 23 is a graph demonstrating the insulinotropic effect of GLP-1 expression in obese db/db mice.
FIG. 24 is a graph demonstrating active plasma GLP-1 levels in obese db/db mice treated with a polynucleotide encoding for modified GLP-1.
FIG. 25 is a graph demonstrating that expression of GLP-1 reduces hyperglycemia in young obese db/db mice.
FIG. 26 is a graph demonstrating that expression of GLP-1 improves glucose tolerance test in young obese db/db mice.
FIG. 27 is a graph demonstrating that expression of GLP-1 lowers blood glucose in obese db/db mice with different starting levels of insulin.
FIG. 28 is a graph demonstrating that expression of GLP-1 improves fasting insulin levels in obese db/db mice.
FIG. 29 is a graph demonstrating that expression of GLP-1 normalizes blood glucose in fed Zucker Diabetic Fatty (ZDF) rats.
FIG. 30 is a graph demonstrating that expression of GLP-1 prevents elevation in fasting blood glucose in Zucker Diabetic Fatty (ZDF) rats.
FIG. 31 is a graph demonstrating the insulinotropic effect of GLP-1 expression in Zucker Diabetic Fatty (ZDF) rats.
FIG. 32 is a graph demonstrating active plasma GLP-1 levels in Zucker Diabetic Fatty (ZDF) rats treated with a polynucleotide encoding for modified GLP-1.
FIG. 33 is a graph demonstrating that expression of GLP-1 prevents elevation of glycated hemoglobin in Zucker Diabetic Fatty (ZDF) rats.
FIG. 34 is a graph demonstrating that expression of GLP-1 decreases food intake in Zucker Diabetic Fatty (ZDF) rats.
FIG. 35 is a graph demonstrating the effects of GLP-1 expression on body weight in Zucker Diabetic Fatty (ZDF) rats.

L149 ANSWER 3 OF 55 IFIPAT COPYRIGHT 2004 IFI on STN DUPLICATE 3

AN	10613785 IFIPAT;IFIUDB;IFICDB
TITLE:	METHOD OF MODIFYING THE RELEASE PROFILE OF SUSTAINED RELEASE COMPOSITIONS
INVENTOR(S):	Burke; Paul A., Oxnard, CA, US Dasch; James R., Needham, MA, US Riley; M. Gary I., Boston, MA, US Steitz-Abadi; Susan A., Barrington, RI, US Zale; Stephen E., Hopkinton, MA, US
PATENT ASSIGNEE(S):	Alkermes Controlled Therapeutics, Inc., Cambridge, MA, 02139, US
AGENT:	HAMILTON, BROOK, SMITH & REYNOLDS, P.C., 530 VIRGINIA ROAD, P.O. BOX 9133, CONCORD, MA, 01742-9133, US

	NUMBER	PK	DATE
PATENT INFORMATION:	US 2004121009	A1	20040624
APPLICATION INFORMATION:	US 2003-681571		20031008

	NUMBER	DATE
PRIORITY APPLN. INFO.:	US 2002-419430P	20021017 (Provisional)
FAMILY INFORMATION:	US 2004121009	20040624

DOCUMENT TYPE:	Utility Patent Application - First Publication
FILE SEGMENT:	CHEMICAL APPLICATION

PARENT CASE DATA:

This application claims the benefit of U.S. Provisional Application No. 60/419,430, filed Oct. 17, 2002. The entire teachings of the above application are incorporated herein by reference.

NUMBER OF CLAIMS: 40 21 Figure(s).

DESCRIPTION OF FIGURES:

FIG. 1 is a graph of serum EPO levels (mU/mL) in rats **administered** EPO-containing microparticles, EPO-containing microparticles admixed with hydrocortisone acetate (5 mg), or EPO-containing microparticles admixed with triamcinolone diacetate (1 mg or 5 mg) over time (days).

FIG. 2 is a graph of hematocrit values (%) in rats **administered** EPO-containing microparticles, EPO-containing microparticles admixed with hydrocortisone acetate (5 mg), or EPO-containing microparticles admixed with triamcinolone diacetate (1 mg or 5 mg) over time (days).

FIG. 3A is a graph of serum EPO levels (mU/ml) in rats **administered** microparticles containing EPO co-encapsulated with hydrocortisone at various levels and EPO-containing microparticles admixed with hydrocortisone acetate (5 mg).

FIG. 3B is a graph of hematocrit values (%) in rats **administered** microparticles containing EPO co-encapsulated with hydrocortisone at various levels (0.25, 2.0, 14%) and EPOcontaining microparticles admixed with hydrocortisone acetate (5 mg) versus time (days).

FIG. 4 is a graph of serum EPO levels (mU/mL) in rats **administered** EPO-containing microparticles in combination with 100 mg of placebo microparticles, 5 mg of triamcinolone acetonide and 100 mg of placebo microparticles admixed or 100 mg of 20% w/w hydrocortisone-containing microparticles over time (days).

FIG. 5 is a graph of hematocrit values (%) in rats **administered** 100 mg of placebo microparticles, 5 mg of triamcinolone acetonide and 100 mg of placebo microparticles admixed or 100 mg of 20% w/w hydrocortisone-containing microparticles over time (days).

FIG. 6A is a graph of the incidence of antibodies to EPO (titer) detected in the serum of rats **administered** a total of 10,000 Units of EPO in combination with a total of 100 mg of placebo microparticles, 5 mg of triamcinolone acetonide and 100 mg of placebo microparticles admixed or 100 mg of 20% w/w hydrocortisone-containing microparticles at day 12 after administration.

FIG. 6B is a graph of the incidence of antibodies to EPO (titer) detected in the serum of rats **administered** a total of 10,000 Units of EPO in combination with a total of 100 mg of placebo microparticles, 5 mg of triamcinolone acetonide and 100 mg of placebo microparticles admixed or 100 mg of 20% w/w hydrocortisone-containing microparticles at day 19 after administration.

FIG. 6C is a graph of the incidence of antibodies to EPO (titer) detected in the serum of rats **administered** a total of 10,000 Units of EPO in combination with a total of 100 mg of placebo microparticles, 5 mg of triamcinolone acetonide and 100 mg of placebo microparticles admixed or 100 mg of 20% w/w hydrocortisone-containing microparticles at day 33 after administration.

FIG. 7A is a graph of serum EPO levels (mU/mL) in rats **administered** EPO-containing microparticles admixed with placebo microparticles, dexamethasone-containing microparticles, budesonide containing microparticles and triamcinolone acetonide-containing microparticles versus time (days).

FIG. 7B is a graph of hematocrit values (%) in rats **administered** EPO-containing microparticles admixed with placebo microparticles, dexamethasone-containing microparticles, budesonide containing microparticles and triamcinolone acetonide-containing microparticles versus time (days).

FIG. 8A is a graph of serum EPO levels (mU/mL) in rats **administered** EPO-containing microparticles admixed with placebo microparticles, triamcinolone acetonide-containing microparticles (5, 10, 20 mg), and budesonide-containing microparticles (25 and 50 mg) as well as microparticles having EPO and triamcinolone acetonide co-encapsulated over time (days).

FIG. 8B is a graph of hematocrit values (%) in rats **administered** EPO-containing microparticles admixed with placebo microparticles, triamcinolone acetonide-containing microparticles (5, 10, 20 mg) and microparticles having EPO and triamcinolone acetonide co-encapsulated (Top Panel), and placebo microparticles and budesonide-containing microparticles (25, 50 mg) (Bottom Panel) over time (days).

FIG. 9 is a graph of serum hFSH levels (mIU/mL) in rats **administered** hFSH-containing microparticles in combination with a total of 75 mg of placebo

microparticles, 10 mg of 2% w/w triamcinolone acetonide-containing microparticles, or 15 mg of 2% w/w hydrocortisone-containing microparticles over time (days).
FIG. 10 is a graph of serum hFSH levels (mIU/mL) in rats **administered** hFSH-containing microparticles in combination with a total of 100 mg of placebo microparticles or 10 mg of 2% triamcinolone acetonide-containing microparticles with 90 mg of placebo microparticles.
FIG. 11 is a graph of serum insulin levels (mU/mL) in rats **administered** 60 mg of insulin-containing microparticles plus 75 mg of placebo, 10 mg of 2% w/w triamcinolone acetonidecontaining microparticles or 15 mg of 2% w/w hydrocortisonecontaining microparticles over time (days).
FIG. 12 is a histogram of osteopontin mRNA expression levels (copy numbers/50 ng cDNA) in rats **administered** 60 mg of insulincontaining microparticles plus 75 mg of placebo, 10 mg of 2% w/ w triamcinolone acetonide-containing microparticles, 15 mg of 2% w/w hydrocortisone-containing microparticles at day 14 after administration.
FIG. 13 is a graph of serum insulin levels (mU/mL) in rats **administered** 60 mg of insulin-containing microparticles plus 25 mg of placebo, 10 mg of 2% w/w triamcinolone acetonidecontaining microparticles or 15 mg of 2% w/w hydrocortisonecontaining microparticles over time (days).
FIG. 14 is a histogram of osteopontin mRNA expression levels (copy numbers/50 ng cDNA) in rats **administered** 60 mg of insulincontaining microparticles plus 25 mg of placebo microparticles, 10 mg of 2% w/w triamcinolone-containing microparticles, 15 mg of 2% w/w hydrocortisone-containing microparticles at days 7 and 35 after administration.
FIG. 15 is a graph of serum exendin-4 levels (pg/mL) in rats ***administered*** 120 mg of exendin-containing microparticles plus 30 mg of placebo microparticles or 10 mg of 2% triamcinolone acetonide-containing microparticles versus time in days.
FIG. 16 is a graph of serum exendin-4 levels (pg/mL) in rats ***administered*** 40 mg of exendin-containing microparticles plus 30 mg of placebo microparticles or 10 mg of 2% triamcinolone acetonide-containing microparticles versus time in days.

AB The present invention relates to a method for the sustained release in vivo of a biologically active labile agent comprising **administering** to a subject in need of treatment an effective amount of a sustained release composition comprising a biocompatible polymer having the biologically active labile agent incorporated therein, and a corticosteroid wherein the labile is released for a period of at least about two weeks. It is understood that the corticosteroid is present in an amount sufficient to modify the release profile of the biologically active labile agent from the sustained release composition. Pharmaceutical compositions suitable for use in the method of the invention are also disclosed.

CLMN 40 21 Figure(s).

FIG. 1 is a graph of serum EPO levels (mU/mL) in rats **administered** EPO-containing microparticles, EPO-containing microparticles admixed with hydrocortisone acetate (5 mg), or EPO-containing microparticles admixed with triamcinolone diacetate (1 mg or 5 mg) over time (days).
FIG. 2 is a graph of hematocrit values (%) in rats **administered** EPO-containing microparticles, EPO-containing microparticles admixed with hydrocortisone acetate (5 mg), or EPO-containing microparticles admixed with triamcinolone diacetate (1 mg or 5 mg) over time (days).
FIG. 3A is a graph of serum EPO levels (mU/ml) in rats **administered** microparticles containing EPO co-encapsulated with hydrocortisone at various levels and EPO-containing microparticles admixed with hydrocortisone acetate (5 mg).
FIG. 3B is a graph of hematocrit values (%) in rats **administered** microparticles containing EPO co-encapsulated with hydrocortisone at various levels (0.25, 2.0, 14%) and EPOcontaining microparticles admixed with hydrocortisone acetate (5 mg) versus time (days).
FIG. 4 is a graph of serum EPO levels (mU/mL) in rats **administered** EPO-containing microparticles in combination with 100 mg of placebo microparticles, 5 mg of triamcinolone acetonide and 100 mg of placebo microparticles admixed or 100 mg of 20% w/w hydrocortisone-containing microparticles over time (days).

FIG. 5 is a graph of hematocrit values (%) in rats **administered** 100 mg of placebo microparticles, 5 mg of triamcinolone acetonide and 100 mg of placebo microparticles admixed or 100 mg of 20% w/w hydrocortisone-containing microparticles over time (days).

FIG. 6A is a graph of the incidence of antibodies to EPO (titer) detected in the serum of rats **administered** a total of 10,000 Units of EPO in combination with a total of 100 mg of placebo microparticles, 5 mg of triamcinolone acetonide and 100 mg of placebo microparticles admixed or 100 mg of 20% w/w hydrocortisone-containing microparticles at day 12 after administration.

FIG. 6B is a graph of the incidence of antibodies to EPO (titer) detected in the serum of rats **administered** a total of 10,000 Units of EPO in combination with a total of 100 mg of placebo microparticles, 5 mg of triamcinolone acetonide and 100 mg of placebo microparticles admixed or 100 mg of 20% w/w hydrocortisone-containing microparticles at day 19 after administration.

FIG. 6C is a graph of the incidence of antibodies to EPO (titer) detected in the serum of rats **administered** a total of 10,000 Units of EPO in combination with a total of 100 mg of placebo microparticles, 5 mg of triamcinolone acetonide and 100 mg of placebo microparticles admixed or 100 mg of 20% w/w hydrocortisone-containing microparticles at day 33 after administration.

FIG. 7A is a graph of serum EPO levels (mU/mL) in rats **administered** EPO-containing microparticles admixed with placebo microparticles, dexamethasone-containing microparticles, budesonide containing microparticles and triamcinolone acetonide-containing microparticles versus time (days).

FIG. 7B is a graph of hematocrit values (%) in rats **administered** EPO-containing microparticles admixed with placebo microparticles, dexamethasone-containing microparticles, budesonide containing microparticles and triamcinolone acetonide-containing microparticles versus time (days).

FIG. 8A is a graph of serum EPO levels (mU/mL) in rats **administered** EPO-containing microparticles admixed with placebo microparticles, triamcinolone acetonide-containing microparticles (5, 10, 20 mg), and budesonide-containing microparticles (25 and 50 mg) as well as microparticles having EPO and triamcinolone acetonide co-encapsulated over time (days).

FIG. 8B is a graph of hematocrit values (%) in rats **administered** EPO-containing microparticles admixed with placebo microparticles, triamcinolone acetonide-containing microparticles (5, 10, 20 mg) and microparticles having EPO and triamcinolone acetonide co-encapsulated (Top Panel), and placebo microparticles and budesonide-containing microparticles (25, 50 mg) (Bottom Panel) over time (days).

FIG. 9 is a graph of serum hFSH levels (mIU/mL) in rats **administered** hFSH-containing microparticles in combination with a total of 75 mg of placebo microparticles, 10 mg of 2% w/w triamcinolone acetonide-containing microparticles, or 15 mg of 2% w/w hydrocortisone-containing microparticles over time (days).

FIG. 10 is a graph of serum hFSH levels (mIU/mL) in rats **administered** hFSH-containing microparticles in combination with a total of 100 mg of placebo microparticles or 10 mg of 2% triamcinolone acetonide-containing microparticles with 90 mg of placebo microparticles.

FIG. 11 is a graph of serum insulin levels (mU/mL) in rats **administered** 60 mg of insulin-containing microparticles plus 75 mg of placebo, 10 mg of 2% w/w triamcinolone acetonidecontaining microparticles or 15 mg of 2% w/w hydrocortisonecontaining microparticles over time (days).

FIG. 12 is a histogram of osteopontin mRNA expression levels (copy numbers/50 ng cDNA) in rats **administered** 60 mg of insulincontaining microparticles plus 75 mg of placebo, 10 mg of 2% w/ w triamcinolone acetonide-containing microparticles, 15 mg of 2% w/w hydrocortisone-containing microparticles at day 14 after administration.

FIG. 13 is a graph of serum insulin levels (mU/mL) in rats **administered** 60 mg of insulin-containing microparticles plus 25 mg of placebo, 10 mg of 2% w/w triamcinolone acetonidecontaining

microparticles or 15 mg of 2% w/w hydrocortisonecontaining microparticles over time (days).

FIG. 14 is a histogram of osteopontin mRNA expression levels (copy numbers/50 ng cDNA) in rats **administered** 60 mg of insulincontaining microparticles plus 25 mg of placebo microparticles, 10 mg of 2% w/w triamcinolone-containing microparticles, 15 mg of 2% w/w hydrocortisone-containing microparticles at days 7 and 35 after administration.

FIG. 15 is a graph of serum exendin-4 levels (pg/mL) in rats **administered** 120 mg of exendin-containing microparticles plus 30 mg of placebo microparticles or 10 mg of 2% triamcinolone acetonide-containing microparticles versus time in days.

FIG. 16 is a graph of serum exendin-4 levels (pg/mL) in rats **administered** 40 mg of exendin-containing microparticles plus 30 mg of placebo microparticles or 10 mg of 2% triamcinolone acetonide-containing microparticles versus time in days.

L149 ANSWER 4 OF 55 IFIPAT COPYRIGHT 2004 IFI on STN DUPLICATE 4

AN	10599325 IFIPAT;IFIUDB;IFICDB		
TITLE:	NOVEL PEPTIDE AGONISTS OF GLP-1 ACTIVITY		
INVENTOR(S):	Larsen; Bjarne Due, Bronshoj, DK Mikkelsen; Jens Damsgaard, Lyngby, DK Neve; Soren, Lyngby, DK		
PATENT ASSIGNEE(S):	Zealand Pharma A/S		
AGENT:	EDWARDS & ANGELL, LLP, P.O. BOX 55874, BOSTON, MA, 02205, US		

	NUMBER	PK	DATE
PATENT INFORMATION:	US 2004106547	A1	20040603
APPLICATION INFORMATION:	US 2002-291226		20021108

	APPLN. NUMBER	DATE	GRANTED PATENT NO. OR STATUS
CONTINUATION OF:	US 2000-614847	20000712	6528486

	NUMBER	DATE	
PRIORITY APPLN. INFO.:	US 1999-143591P	19990712	(Provisional)
FAMILY INFORMATION:	US 2004106547	20040603	
	US 6528486		
DOCUMENT TYPE:	Utility Patent Application - First Publication		
FILE SEGMENT:	CHEMICAL APPLICATION		
NUMBER OF CLAIMS:	48 8 Figure(s).		

DESCRIPTION OF FIGURES:

FIG. 1 shows the effect of Compound 1 (SEQ ID NO:101) (des Pro36exendin-4(1-39)-NH2) on blood glucose levels of mice, cf. Example 25.

FIG. 2 shows the effect of Compound 2 (SEQ ID NO:93) (des Pro36exendin-4(1-39)-Lys6-NH2 on the blood glucose levels of mice, cf. Example 25.

FIG. 3 shows the effect of Compound 5 (SEQ ID NO:89) (Gly8, Lys37(palmitoyl)-GLP1-(7-36)(Human)-(Lys)7-NH2 on the blood glucose levels of mice, cf. Example 25.

FIG. 4 shows in vivo degradation kinetics in rabbits after i.v. injection of 1 mu mol/kg of Compound 4 and Compound (iii), cf. Example 27.

FIG. 5 is a plot of AUC (area under the curve) values (mean+-SEM) for Compounds 2, 14-16, 18 and 19 in an oral glucose tolerance test (OGTT), cf. Example 28.

FIG. 6 shows a synthetic cDNA constructed for heterolog expression of Compound 2 in yeast. The new construct was designated pYES0010, cf. Example 20.

FIG. 7 is a plot of dose-response on GTT in db/db mice based on relative AUC0-240 min values (mean+-SEM) for Compound 2 and Compound (i), cf. Example 29.

FIG. 8 shows the effects of a maximal dose of Compound 2, i.e. 100 nmol/kg

i.p., on the oral glucose tolerance test (OGTT) when **administered** up to 24 hours before the OGTT.

AB Novel peptide agonists of GLP-1 activity useful for lowering blood glucose levels. The novel peptides comprise variants of the GLP-1 or the exendin-4 polypeptide sequence and are pharmacologically active and stable. These peptides are useful in the treatment of diseases that benefit from regulation of excess levels of blood glucose and/or regulation of gastric emptying, such as diabetes and eating disorders.

CLMN 48 8 Figure(s).

FIG. 1 shows the effect of Compound 1 (SEQ ID NO:101) (des Pro36exendin-4(1-39)-NH2) on blood glucose levels of mice, cf. Example 25.

FIG. 2 shows the effect of Compound 2 (SEQ ID NO:93) (des Pro36exendin-4(1-39)-Lys6-NH2 on the blood glucose levels of mice, cf. Example 25.

FIG. 3 shows the effect of Compound 5 (SEQ ID NO:89) (Gly8, Lys37(palmitoyl)-GLP1-(7-36)(Human)-(Lys)7-NH2 on the blood glucose levels of mice, cf. Example 25.

FIG. 4 shows in vivo degradation kinetics in rabbits after i.v. injection of 1 mu mol/kg of Compound 4 and Compound (iii), cf. Example 27.

FIG. 5 is a plot of AUC (area under the curve) values (mean+-SEM) for Compounds 2, 14-16, 18 and 19 in an oral glucose tolerance test (OGTT), cf. Example 28.

FIG. 6 shows a synthetic cDNA constructed for heterolog expression of Compound 2 in yeast. The new construct was designated pYES0010, cf. Example 20.

FIG. 7 is a plot of dose-response on GTT in db/db mice based on relative AUC0-240 min values (mean+-SEM) for Compound 2 and Compound (i), cf. Example 29.

FIG. 8 shows the effects of a maximal dose of Compound 2, i.e. 100 nmol/kg i.p., on the oral glucose tolerance test (OGTT) when **administered** up to 24 hours before the OGTT.

L149 ANSWER 5 OF 55 IFIPAT COPYRIGHT 2004 IFI on STN DUPLICATE 5

AN 10585221 IFIPAT;IFIUDB;IFICDB

TITLE: LONG-ACTING EXENDINS AND EXENDIN AGONISTS

INVENTOR(S): Fridkin; Matityahu, Rehovot, IL
Shechter; Yoram, Rehovot, IL
Tsubery; Haim, El-Ad, IL

PATENT ASSIGNEE(S): YEDA Research and Development Co., Ltd, The Weizmann Institute of Science,, PO Box 95, Rehovot, 76100, IL

AGENT: BROWDY AND NEIMARK, P.L.L.C.;624 NINTH STREET, NW, SUITE 300, WASHINGTON, DC, 20001-5303, US

	NUMBER	PK	DATE
PATENT INFORMATION:	US 2004092443	A1	20040513
APPLICATION INFORMATION:	US 2003-408262		20030408

	APPLN. NUMBER	DATE	GRANTED PATENT NO. OR STATUS
CONTINUATION OF:	US 1999-242026	19990205	6504005
CONTINUATION-IN-PART OF:	US 2003-336839	20030106	PENDING

	NUMBER	DATE
PRIORITY APPLN. INFO.:	IL 1996-119029	19960806
FAMILY INFORMATION:	US 2004092443	20040513
	US 6504005	

DOCUMENT TYPE: Utility
Patent Application - First Publication

FILE SEGMENT: CHEMICAL
APPLICATION

PARENT CASE DATA:

The present application is a continuation-in-part application of copending U.S. application Ser. No. 10/336,839, filed Jan. 6, 2003, which is a continuation of U.S. application Ser. No. 09/ 242,026, filed Feb. 5, 1999, now U.S. Pat. No. 6,504,005, granted Jan. 7, 2003. The U.S. application Ser. No. 09/242,026 claimed priority benefit under 35 U.S.C. 371 of PCT/IL97/00265, filed Aug. 5, 1997, and claimed priority benefit under 35 U.S.C. 119 of Israeli Patent Application No. 119029, filed Aug. 6, 1996. The contents of each of applications No. 10/336,839 and No. 09/242,026 is hereby incorporated herein by reference in its entirety.

NUMBER OF CLAIMS: 19 5 Figure(s).

DESCRIPTION OF FIGURES:

FIG. 1 is a graph showing the rate of FMS-hydrolysis from (FMS)3exendin-4 at pH 8.5, 37 degrees C. A solution of (FMS)3-**exendin4** (0.07 mM in 0.1 M NaHCO3, pH 8.5) was incubated at 37 degrees C. At the indicated time points, aliquots (0.4 ml) were withdrawn and free amino side chains were quantitated with 2,4, 6-trinitrobenzenesulfonic acid (TNBS).

FIG. 2 is a graph showing glucose-lowering pattern of native exendin-4 ***administered*** subcutaneously to CD1 mice, at 5 indicated concentrations (exendin-4 was dissolved in 0.1 ml PBS buffer, 0.1% BSA). At the indicated time points, circulating glucose levels were determined. Each experimental group consisted of five mice. t1/2 values are indicated for each concentration of exendin-4. Data are presented as means+-SE.

FIG. 3 is a graph showing the intrinsic glucose-lowering potency of (FMS)3-exendin-4 prior to FMS hydrolysis compared to native exendin-4. The indicated concentrations of native-exendin-4 and of (FMS)3-exendin-4 were ***administered*** subcutaneously to CD 1 mice (n=5 per each group). Circulating glucose levels were determined one hour after administration. Results are expressed as % of maximal glucose-lowering capacity, where 100% is the effect manifested by **administering** 1 mu g (250 picomoles) of native exendin-4 per mouse.

FIG. 4 is a graph showing glucose-lowering patterns of (FMS)3exendin-4 following subcutaneous administration to CD1 mice, at 1, 10 and 100 mu g/mouse (n=5 per each group). Circulating glucose levels were monitored at the indicated time points after administration. t1/2 values are indicated for each concentration of exendin-4. Data are presented as means+-SE.

FIG. 5 is a graph showing glucose-lowering patterns of native exendin-4 and (FMS)3-exendin-4, following a single subcutaneous administration to db/db mice. Three groups of db/db mice (n=4 per group) were **administered** subcutaneously either with saline, native exendin-4 (10 mu g/mouse), or (FMS)3-exendin-4 (10 mu g/ mouse). Circulating glucose levels were then monitored. Results are expressed as percent decrease in plasma glucose concentration in the exendin-4- and the (FMS)3-exendin-4treated groups relative to saline-treated group, measured at the same time point during the day.

AB Long-acting exendin or exendin agonist derivatives of the formula (X)n-Z are provided, wherein X is a radical 9fluorenylmethoxycarbonyl (Fmoc) or 2-sulfo-9-fluorenylmethoxycarbonyl (FMS), Z is the residue of an exendin or exendin agonist linked to the radical X through an amino or hydroxyl group, and n is 1 to 3. The exendin is exendin-3 or exendin-4. The derivatives are useful for prevention or treatment of conditions, diseases or disorders that can be treated by an exendin, for example for prevention of hyperglycemia and for treatment of diabetes mellitus, e.g. noninsulin dependent diabetes mellitus, insulin-dependent diabetes mellitus, and gestational diabetes mellitus.

CLMN 19 5 Figure(s).

FIG. 1 is a graph showing the rate of FMS-hydrolysis from (FMS)3exendin-4 at pH 8.5, 37 degrees C. A solution of (FMS)3-**exendin4** (0.07 mM in 0.1 M NaHCO3, pH 8.5) was incubated at 37 degrees C. At the indicated time points, aliquots (0.4 ml) were withdrawn and free amino side chains were quantitated with 2,4, 6-trinitrobenzenesulfonic acid (TNBS).

FIG. 2 is a graph showing glucose-lowering pattern of native exendin-4 **administered** subcutaneously to CD1 mice, at 5 indicated concentrations (exendin-4 was dissolved in 0.1 ml PBS buffer, 0.1% BSA). At the indicated time points, circulating glucose levels were determined. Each experimental group consisted of five mice. t1/2 values are indicated

for each concentration of exendin-4. Data are presented as means+-SE.

FIG. 3 is a graph showing the intrinsic glucose-lowering potency of (FMS)3-exendin-4 prior to FMS hydrolysis compared to native exendin-4. The indicated concentrations of native-exendin-4 and of (FMS)3-exendin-4 were **administered** subcutaneously to CD 1 mice (n=5 per each group). Circulating glucose levels were determined one hour after administration. Results are expressed as % of maximal glucose-lowering capacity, where 100% is the effect manifested by **administering** 1 mu g (250 picomoles) of native exendin-4 per mouse.

FIG. 4 is a graph showing glucose-lowering patterns of (FMS)3exendin-4 following subcutaneous administration to CD1 mice, at 1, 10 and 100 mu g/mouse (n=5 per each group). Circulating glucose levels were monitored at the indicated time points after administration. t1/2 values are indicated for each concentration of exendin-4. Data are presented as means+-SE.

FIG. 5 is a graph showing glucose-lowering patterns of native exendin-4 and (FMS)3-exendin-4, following a single subcutaneous administration to db/db mice. Three groups of db/db mice (n=4 per group) were **administered** subcutaneously either with saline, native exendin-4 (10 mu g/mouse), or (FMS)3-exendin-4 (10 mu g/ mouse). Circulating glucose levels were then monitored. Results are expressed as percent decrease in plasma glucose concentration in the exendin-4- and the (FMS)3-exendin-4treated groups relative to saline-treated group, measured at the same time point during the day.

L149 ANSWER 6 OF 55 IFIPAT COPYRIGHT 2004 IFI on STN DUPLICATE 6

AN 10565515 IFIPAT;IFIUDB;IFICDB

TITLE: BICYCLIC OLIGOPEPTIDES

INVENTOR(S): Mack; Juergen, Biberach, DE
Maurer; Till, Oberstadion, DE
Peters; Stefan, Biberach, DE
Potterat; Olivier, Mittelbiberach, DE
Streicher; Ruediger, Biberach, DE
Wagner; Klaus, Warthausen, DE

PATENT ASSIGNEE(S): Boehringer Ingelheim Pharma GmbH & Co. KG, Binger Strasse 173, Ingelheim, 55216, DE

AGENT: BOEHRINGER INGELHEIM CORPORATION, 900 RIDGEBURY ROAD, P. O. BOX 368, RIDGEFIELD, CT, 06877, US

	NUMBER	PK	DATE
PATENT INFORMATION:	US 2004072736	A1	20040415
APPLICATION INFORMATION:	US 2003-621272		20030717

	NUMBER	DATE
PRIORITY APPLN. INFO.:	US 2002-416797P	20021008 (Provisional)
FAMILY INFORMATION:	US 2004072736	20040415

DOCUMENT TYPE: Utility
Patent Application - First Publication

FILE SEGMENT: CHEMICAL
APPLICATION

PARENT CASE DATA:

Benefit of U.S. Provisional Application Serial No. 60/416,797, filed on Oct. 8, 2002 is hereby claimed, and said Application is herein incorporated by reference.

NUMBER OF CLAIMS: 17

AB The invention relates to a bicyclic oligopeptide or ester thereof having the capability to inhibit the glucagon receptor, comprised of: (a) a first cyclic group, which comprises at least one cysteine group and is formed by an amide bonding of the N-terminal amino acid with the second carboxylate group of a diacid amino acid, and (b) a second cyclic group which is formed by an amide bonding of an amino acid with the alpha

-carboxylate group of said diacid amino acid, and by a disulfide bonding of the C-terminal cysteine and a cysteine group within the first cyclic group (a) ; and to the use of such bicyclic oligopeptides for the preparation of a medicament for the treatment or prevention of diseases, in which glucagon receptors are involved.
CLMN 17

L149 ANSWER 7 OF 55 IFIPAT COPYRIGHT 2004 IFI on STN DUPLICATE 7
AN 10495267 IFIPAT;IFIUDB;IFICDB
TITLE: METHODS OF TREATING DIABETES AND OTHER BLOOD SUGAR DISORDERS
INVENTOR(S): Armentano; Donna, Belmont, MA, US
Gregory; Richard J., Westford, MA, US
Parsons; Geoffrey, Jamaica Plain, MA, US
Wadsworth; Samuel C., Shrewsbury, MA, US
PATENT ASSIGNEE(S): Genzyme Corporation, Cambridge, MA, 02139, US
AGENT: GENZYME CORPORATION LEGAL DEPARTMENT, 15 PLEASANT ST CONNECTOR, FRAMINGHAM, MA, 01701-9322, US

	NUMBER	PK	DATE
PATENT INFORMATION:	US 2004002468	A1	20040101
APPLICATION INFORMATION:	US 2002-215272		20020807

	NUMBER	DATE
PRIORITY APPLN. INFO.:	US 2001-310982P	20010808 (Provisional)
FAMILY INFORMATION:	US 2004002468	20040101

DOCUMENT TYPE: Utility
Patent Application - First Publication
FILE SEGMENT: CHEMICAL
APPLICATION

PARENT CASE DATA:

This application claims the benefit of U.S. Provisional Application No. 60/310,982, filed Aug. 8, 2001. The entire teachings of the above application(s) are incorporated herein by reference.

NUMBER OF CLAIMS: 22 18 Figure(s).
DESCRIPTION OF FIGURES:
FIG. 1 shows the nucleotide (SEQ ID NO: 1) and amino acid (SEQ ID NO: 2) sequences of the signal peptide from secreted human alkaline phosphatase (SEAP) linked to Gly-8 modified human GLP1 (GLP-1-Gly-8), designated SEAP.GLP-1Gly8.
FIG. 2 shows the nucleotide (SEQ ID NO: 3) and amino acid (SEQ ID NO: 4) sequences of the leader from proexendin-4 linked to GLP-1-Gly-8, designated Exendin-4.GLP-1Gly8.
FIG. 3 shows the nucleotide (SEQ ID NO: 5) and amino acid (SEQ ID NO: 6) sequences of the leader from pro-helodermin linked to GLP-1-Gly-8, designated Helodermin.GLP-1 Gly8.
FIG. 4 shows the nucleotide (SEQ ID NO: 7) and amino acid (SEQ ID NO: 8) sequences of the leader from pro-glucose dependent insulinotropic polypeptide (GIP) linked to GLP-1-Gly-8, designated GIP.GLP-1Gly8.
FIG. 5 shows the nucleotide (SEQ ID NO: 9) and amino acid (SEQ ID NO: 10) sequences of the leader from pro-insulin-like growth factor 1 (IGF1) linked to GLP-1-Gly-8 via a consensus furin cleavage site, designated IGF-1 (furin).GLP-1Gly8.
FIG. 6 shows the nucleotide (SEQ ID NO: 11) and amino acid (SEQ ID NO: 12) sequences of the leader from pro-insulin-like growth factor 1 (IGF1) linked to GLP-1-Gly-8, designated IGF-1.GLP1Gly8.
FIG. 7 shows the nucleotide (SEQ ID NO: 13) and amino acid (SEQ ID NO: 14) sequences of the leader from preproglucagon linked to GLP-1-Gly-8, designated Preproglucagon.GLP-1 Gly8.
FIG. 8 shows the nucleotide (SEQ ID NO: 15) and amino acid (SEQ ID NO: 16) sequences of the leader from alpha-1 antitrypsin linked to GLP-1-Gly-8, designated Alpha-1 antitrypsin.GLP-1 Gly8.

FIG. 9 shows the nucleotide (SEQ ID NO: 17) and amino acid (SEQ ID NO: 18) sequences of amino acids 1-46 of human factor IX which contains a signal peptide and a cleavage site for a prohormone convertase linked to GLP-1-Gly-8, designated Factor IX.GLP-1Gly8.
FIG. 10 shows the nucleotide (SEQ ID NO: 19) and amino acid (SEQ ID NO: 20) sequences of the leader from proexendin-4 linked to GLP-1-Gly-8 via the cleavage site of IGF-1, designated **Exendin4** (IGF-1).GLP-1Gly8.
FIG. 11 are schematics of the IGF-1.GLP-1Gly8, the Preproglucagon.GLP-1Gly8, the Alpha-1 antitrypsin.GLP-1Gly8, Exendin-4.GLP-1Gly8, the Exendin-4 (IGF-1).GLP-1Gly8, and the Factor IX.GLP-1Gly8.
FIG. 12 is a bar graph showing GLP-1 expression levels in the supernatant of 293 cells transfected with SEAP.GLP-1Gly8, Exendin-4.GLP-1Gly8, Helodermin.GLP-1Gly8, GIP.GLP-1Gly8, IGF1(furin).GLP-1Gly8 or a control (mock).
FIG. 13 is a bar graph showing GLP-1 expression levels in the supernatant of 293 cells transfected with Alpha-1 antitrypsin. GLP-1Gly8, Preproglucagon.GLP-1Gly8, IGF-1.GLP-1Gly8, Exendin-4. GLP-1Gly8 or Exendin-4 (IGF-1).GLP-1Gly8.
FIG. 14 is a bar graph showing GLP-1 secreted from C2C12 cells transfected with Exendin-4.GLP-1Gly8, Exendin-4 (IGF-1).GLP1Gly8 or Factor IX.GLP-1Gly8.
FIG. 15 is a graph showing the plasma concentrations of GLP-1 in mice transduced with GLP-1 expression plasmids by high-volume tail vein injection.
FIG. 16 is a graph showing the blood glucose levels of obese db/ db mice and their lean littermates that were treated with a high volume injection of plasmid DNA coding for **exendin4** GLP-1 under the control of the CMV enhancer/ubiquitin promoter.
FIG. 17 is a graph showing inducible expression of GLP-1 using the Valentis Gene Switch System.
FIGS. 18A-18B list examples of modified GLP-1.

AB Compositions, expression vectors and host cells comprising nucleic acid which encodes a precursor glucagon-like peptide 1 (GLP-1) comprising mammalian GLP-1 linked to a heterologous signal sequence are encompassed by the present invention. The invention also relates to a method of promoting insulin production in an individual comprising administering to the individual an effective amount of a nucleic acid encoding a precursor GLP-1. The present invention also relates to a method of treating an individual having a blood sugar defect (e.g., type I or type II diabetes), comprising administering to the individual an effective amount of a nucleic acid encoding the precursor GLP-1. In a particular embodiment, the invention pertains to a method of treating an individual having a blood sugar defect comprising administering to the individual an effective amount of a nucleic acid encoding a precursor GLP-1 wherein the precursor GLP-1 comprises a signal sequence which codes for precursor cleavage at the activation cleavage site of the precursor GLP-1.

CLMN 22 18 Figure(s).

FIG. 1 shows the nucleotide (SEQ ID NO: 1) and amino acid (SEQ ID NO: 2) sequences of the signal peptide from secreted human alkaline phosphatase (SEAP) linked to Gly-8 modified human GLP1 (GLP-1-Gly-8), designated SEAP.GLP-1Gly8.
FIG. 2 shows the nucleotide (SEQ ID NO: 3) and amino acid (SEQ ID NO: 4) sequences of the leader from proexendin-4 linked to GLP-1-Gly-8, designated Exendin-4.GLP-1Gly8.
FIG. 3 shows the nucleotide (SEQ ID NO: 5) and amino acid (SEQ ID NO: 6) sequences of the leader from pro-helodermin linked to GLP-1-Gly-8, designated Helodermin.GLP-1 Gly8.
FIG. 4 shows the nucleotide (SEQ ID NO: 7) and amino acid (SEQ ID NO: 8) sequences of the leader from pro-glucose dependent insulinotropic polypeptide (GIP) linked to GLP-1-Gly-8, designated GIP.GLP-1Gly8.
FIG. 5 shows the nucleotide (SEQ ID NO: 9) and amino acid (SEQ ID NO: 10) sequences of the leader from pro-insulin-like growth factor 1 (IGF1) linked to GLP-1-Gly-8 via a consensus furin cleavage site, designated IGF-1 (furin).GLP-1Gly8.
FIG. 6 shows the nucleotide (SEQ ID NO: 11) and amino acid (SEQ ID NO: 12) sequences of the leader from pro-insulin-like growth factor 1 (IGF1) linked to GLP-1-Gly-8, designated IGF-1.GLP1Gly8.
FIG. 7 shows the nucleotide (SEQ ID NO: 13) and amino acid (SEQ ID NO: 14) sequences of the leader from preproglucagon linked to GLP-1-Gly-8, designated Preproglucagon.GLP-1 Gly8.

FIG. 8 shows the nucleotide (SEQ ID NO: 15) and amino acid (SEQ ID NO: 16) sequences of the leader from alpha-1 antitrypsin linked to GLP-1-Gly-8, designated Alpha-1 antitrypsin.GLP-1 Gly8.

FIG. 9 shows the nucleotide (SEQ ID NO: 17) and amino acid (SEQ ID NO: 18) sequences of amino acids 1-46 of human factor IX which contains a signal peptide and a cleavage site for a prohormone convertase linked to GLP-1-Gly-8, designated Factor IX.GLP-1Gly8.

FIG. 10 shows the nucleotide (SEQ ID NO: 19) and amino acid (SEQ ID NO: 20) sequences of the leader from proexendin-4 linked to GLP-1-Gly-8 via the cleavage site of IGF-1, designated **Exendin4** (IGF-1).GLP-1Gly8.

FIG. 11 are schematics of the IGF-1.GLP-1Gly8, the Preproglucagon.GLP-1Gly8, the Alpha-1 antitrypsin.GLP-1Gly8, Exendin-4.GLP-1Gly8, the Exendin-4 (IGF-1).GLP-1Gly8, and the Factor IX.GLP-1Gly8.

FIG. 12 is a bar graph showing GLP-1 expression levels in the supernatant of 293 cells transfected with SEAP.GLP-1Gly8, Exendin-4.GLP-1Gly8, Helodermin.GLP-1Gly8, GIP.GLP-1Gly8, IGF1(furin).GLP-1Gly8 or a control (mock).

FIG. 13 is a bar graph showing GLP-1 expression levels in the supernatant of 293 cells transfected with Alpha-1 antitrypsin. GLP-1Gly8, Preproglucagon.GLP-1Gly8, IGF-1.GLP-1Gly8, Exendin-4. GLP-1Gly8 or Exendin-4 (IGF-1).GLP-1Gly8.

FIG. 14 is a bar graph showing GLP-1 secreted from C2C12 cells transfected with Exendin-4.GLP-1Gly8, Exendin-4 (IGF-1).GLP1Gly8 or Factor IX.GLP-1Gly8.

FIG. 15 is a graph showing the plasma concentrations of GLP-1 in mice transduced with GLP-1 expression plasmids by high-volume tail vein injection.

FIG. 16 is a graph showing the blood glucose levels of obese db/ db mice and their lean littermates that were treated with a high volume injection of plasmid DNA coding for **exendin4** GLP-1 under the control of the CMV enhancer/ubiquitin promoter.

FIG. 17 is a graph showing inducible expression of GLP-1 using the Valentis Gene Switch System.

FIGS. 18A-18B list examples of modified GLP-1.

L149 ANSWER 8 OF 55 IFIPAT COPYRIGHT 2004 IFI on STN DUPLICATE 8

AN	04031531 IFIPAT;IFIUDB;IFICDB
TITLE:	INOTROPIC AND DIURETIC EFFECTS OF EXENDIN AND GLP-1
INVENTOR(S):	Beeley; Nigel R. A., Solana Beach, CA Prickett; Kathryn, San Diego, CA Vine; Will, Poway, CA Young; Andrew A., San Diego, CA
PATENT ASSIGNEE(S):	Amylin Pharmaceuticals, Inc., San Diego, CA, US
PRIMARY EXAMINER:	Lankford, Jr., Leon B
AGENT:	Arnold & Porter

	NUMBER	PK	DATE	
PATENT INFORMATION:	US 6703359	B1	20040309	
	WO 9940788		19990819	
APPLICATION INFORMATION:	US 2000-622105		20000922	
	WO 1999-US2554		19990205	
			20000922	PCT 371 date
			20000922	PCT 102(e) date

	NUMBER	DATE	
PRIORITY APPLN. INFO.:	US 1998-75122P	19980213	(Provisional)
FAMILY INFORMATION:	US 6703359	20040309	

DOCUMENT TYPE:	Utility Granted Patent - Utility, no Pre-Grant Publication
FILE SEGMENT:	CHEMICAL GRANTED

PARENT CASE DATA:

This application claims the benefit of Provisional application Ser. No. 60/075,122, filed Feb. 13, 1998.

NUMBER OF CLAIMS: 42
GRAPHICS INFORMATION: 10 Drawing Sheet(s), 18 Figure(s).
DESCRIPTION OF FIGURES:

FIG. 1(A-B) is a graphical depiction of the response of mean arterial pressure (MAP) to GLP-1. (A) MAP is presented as % of predose values measured over the 30 minutes prior to drug administration; (B) Dose-response curve for effects of GLP-1 of MAP. The response plotted is the incremental area under the curve from 0 to 2 hours after the bolus dose.

FIG. 2 is a graphical depiction of the inotropic response to GLP1. The rate of change of blood pressure (dP/dt) is indicative of cardiac contractility, which increased in response to a subcutaneous injection of GLP-1 given to conscious rats.

FIG. 3(A-B) is a graphical depiction of the response of urine flow to intravenous bolus doses of GLP-1. (A) Urine flow was measured at 15 minute intervals and presented as % of predose values measured over the 30 minutes prior to drug administration; (B) Dose-response curve for effects of GLP-1 on urine flow. The response plotted is the percent change in flow from 0 to 15 minutes after the bolus dose relative to the flow over the previous 30 minutes.

FIG. 4(A-B) is a graphical depiction of the response of sodium excretion to intravenous bolus doses of GLP-1. (A) Sodium excretion was measured at 15 minute intervals and presented as % of predose values measured over the 30 minutes prior to drug administration; (B) Dose-response curve for effects of GLP-1 on sodium excretion. The response plotted is the percent change in sodium excretion from 0 to 15 minutes after the bolus dose relative to excretion over the previous 30 minutes.

FIG. 5(A-B) is a graphical depiction of the response of urinary potassium concentration to intravenous bolus doses of GLP-1. (A) Urinary potassium concentration was measured at 15 minute intervals and presented as % of predose values measured over the 30 minutes prior to drug administration; (B) Dose-response curve for effects of GLP-1 on urinary potassium concentration. The response plotted is the percent change in urinary potassium concentration from 0 to 15 minutes after the bolus dose relative to the urinary potassium concentration over the previous 30 minutes.

FIG. 6(A-B) is a graphical depiction of the response of mean arterial pressure (MAP) to exendin 4. (A) MAP is presented as % of predose values measured over the 30 minutes prior to drug administration; (B) Dose-response curve for effects of exendin on MAP. The response plotted is the incremental area under the curve from 0 to 2 hours after the bolus dose.

FIG. 7 is a graphical depiction of the inotropic response to exendin-4. The rate of change of blood pressure (dP/dt) is indicative of cardiac contractility, which increased in response to a subcutaneous injection of exendin-4 given to conscious rats.

FIG. 8(A-B) is a graphical depiction of the response of urine flow to intravenous bolus doses of exendin-4. (A) Urine flow was measured at 15 minute intervals; (B) Dose-response curve for effects of exendin-4 on urine flow. The response plotted is urine flow from 0 to 15 minutes after the bolus dose.

FIG. 9(A-B) is a graphical depiction of the response of sodium excretion to intravenous bolus doses of exendin-4. (A) Sodium excretion was measured at 15 minute intervals and presented as % of predose values measured over the 30 minutes prior to drug administration; (B) Dose-response curve for effects of ***exendin4*** on sodium excretion. The response plotted is the percent change in sodium excretion from 0 to 15 minutes after the bolus dose relative to excretion over the previous 30 minutes.

FIG. 10(A-B) is a graphical depiction of the response of urinary potassium concentration to intravenous bolus doses of exendin-4. (A) Urinary potassium concentration was measured at 15 minute intervals and presented as % of predose values measured over the 30 minutes prior to exendin-4 administration; (B) Doseresponse curve for effects of exendin on urinary potassium concentration. The response plotted is the incremental area under the curve from 0 to 2 hours after the bolus dose.

AB Methods for increasing urine flow are disclosed, comprising administration of an effective amount of GLP-1, an exendin, or an exendin

or GLP-1 agonist. Methods for increasing urinary sodium excretion and decreasing urinary potassium concentration are also disclosed. The methods are useful for treating conditions or disorders associated with toxic hypervolemia,such as renal failure, congestive heart failure, nephrotic syndrome, cirrhosis, pulmonary edema, and hypertension. The present invention also relates to methods for inducing an inotropic response comprising administration of an effective amount of GLP-1, an exendin, or an exendin or GLP-1 agonist. These methods are useful for treating conditions or disorders that can be alleviated by an increase in cardiac contractility such as congestive heart failure. Pharmaceutical compositions for use in the methods of the invention are also disclosed.

CLMN 42

GI 10 Drawing Sheet(s), 18 Figure(s).

FIG. 1(A-B) is a graphical depiction of the response of mean arterial pressure (MAP) to GLP-1. (A) MAP is presented as % of predose values measured over the 30 minutes prior to drug administration; (B) Dose-response curve for effects of GLP-1 of MAP. The response plotted is the incremental area under the curve from 0 to 2 hours after the bolus dose.

FIG. 2 is a graphical depiction of the inotropic response to GLP1. The rate of change of blood pressure (dP/dt) is indicative of cardiac contractility, which increased in response to a subcutaneous injection of GLP-1 given to conscious rats.

FIG. 3(A-B) is a graphical depiction of the response of urine flow to intravenous bolus doses of GLP-1. (A) Urine flow was measured at 15 minute intervals and presented as % of predose values measured over the 30 minutes prior to drug administration; (B) Dose-response curve for effects of GLP-1 on urine flow. The response plotted is the percent change in flow from 0 to 15 minutes after the bolus dose relative to the flow over the previous 30 minutes.

FIG. 4(A-B) is a graphical depiction of the response of sodium excretion to intravenous bolus doses of GLP-1. (A) Sodium excretion was measured at 15 minute intervals and presented as % of predose values measured over the 30 minutes prior to drug administration; (B) Dose-response curve for effects of GLP-1 on sodium excretion. The response plotted is the percent change in sodium excretion from 0 to 15 minutes after the bolus dose relative to excretion over the previous 30 minutes.

FIG. 5(A-B) is a graphical depiction of the response of urinary potassium concentration to intravenous bolus doses of GLP-1. (A) Urinary potassium concentration was measured at 15 minute intervals and presented as % of predose values measured over the 30 minutes prior to drug administration; (B) Dose-response curve for effects of GLP-1 on urinary potassium concentration. The response plotted is the percent change in urinary potassium concentration from 0 to 15 minutes after the bolus dose relative to the urinary potassium concentration over the previous 30 minutes.

FIG. 6(A-B) is a graphical depiction of the response of mean arterial pressure (MAP) to exendin 4. (A) MAP is presented as % of predose values measured over the 30 minutes prior to drug administration; (B) Dose-response curve for effects of exendin on MAP. The response plotted is the incremental area under the curve from 0 to 2 hours after the bolus dose.

FIG. 7 is a graphical depiction of the inotropic response to exendin-4. The rate of change of blood pressure (dP/dt) is indicative of cardiac contractility, which increased in response to a subcutaneous injection of exendin-4 given to conscious rats.

FIG. 8(A-B) is a graphical depiction of the response of urine flow to intravenous bolus doses of exendin-4. (A) Urine flow was measured at 15 minute intervals; (B) Dose-response curve for effects of exendin-4 on urine flow. The response plotted is urine flow from 0 to 15 minutes after the bolus dose.

FIG. 9(A-B) is a graphical depiction of the response of sodium excretion to intravenous bolus doses of exendin-4. (A) Sodium excretion was measured at 15 minute intervals and presented as % of predose values measured over the 30 minutes prior to drug administration; (B) Dose-response curve for effects of **exendin4** on sodium

excretion. The response plotted is the percent change in sodium excretion from 0 to 15 minutes after the bolus dose relative to excretion over the previous 30 minutes.

FIG. 10(A-B) is a graphical depiction of the response of urinary potassium concentration to intravenous bolus doses of exendin-4. (A) Urinary potassium concentration was measured at 15 minute intervals and presented as % of predose values measured over the 30 minutes prior to exendin-4 administration; (B) Doseresponse curve for effects of exendin on urinary potassium concentration. The response plotted is the incremental area under the curve from 0 to 2 hours after the bolus dose.

L149 ANSWER 9 OF 55 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2004:41516 CAPLUS
DOCUMENT NUMBER: 140:105831
TITLE: Pharmaceutical compositions and uses of GLP-1 mimetics for the treatment of diabetes
INVENTOR(S): Steiness, Eva
PATENT ASSIGNEE(S): Zealand Pharma A/S, Den.
SOURCE: PCT Int. Appl., 68 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2004005342	A1	20040115	WO 2003-DK463	20030702

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

PRIORITY APPLN. INFO.: US 2002-393917P P 20020704
US 2003-465613P P 20030424

AB The present invention relates to use of GLP-1 or a related mol. having GLP-effect for the manufacture of a medicament for preventing or treating diabetes in a mammal. The amount and timing of administration of said medicament are subsequently reduced to produce a 'drug holiday'. Practice of the invention achieves effective therapy without continuous drug exposure and without continuous presence of therapeutic levels of the drug. The invention also discloses a method of treating diabetes and related disorders in a mammal by **administering** glucagon like peptide (GLP-1) or a related mol. having GLP-1 like effect and thereby providing a therapeutically effective amount of endogenous insulin.

REFERENCE COUNT: 12 THERE ARE 12 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L149 ANSWER 10 OF 55 USPATFULL on STN
ACCESSION NUMBER: 2004:178930 USPATFULL
TITLE: Long lasting synthetic glucagon like peptide (GLP-1)
INVENTOR(S): Bridon, Dominique, Ville Mont-Royal, CANADA
L' Archeveque, Benoit, Laval, CANADA
Ezrin, Alan M., Moraga, CA, UNITED STATES
Holmes, Darren L., Montreal, CANADA
Leblanc, Anouk, Montreal, CANADA
St. Pierre, Serge, Ile Bizard, CANADA
PATENT ASSIGNEE(S): CONJUCHEM, INC., Montreal, CANADA (non-U.S. corporation)

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 2004138100	A1	20040715
APPLICATION INFO.:	US 2003-723099	A1	20031125 (10)

RELATED APPLN. INFO.: Continuation of Ser. No. US 2002-288340, filed on 4 Nov 2002, PENDING Division of Ser. No. US 2000-657332, filed on 7 Sep 2000, GRANTED, Pat. No. US 6514500

	NUMBER	DATE
PRIORITY INFORMATION:	US 1999-159783P	19991015 (60)

DOCUMENT TYPE: Utility
FILE SEGMENT: APPLICATION
LEGAL REPRESENTATIVE: MORRISON & FOERSTER LLP, 425 MARKET STREET, SAN FRANCISCO, CA, 94105-2482
NUMBER OF CLAIMS: 19
EXEMPLARY CLAIM: 1
LINE COUNT: 2120
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB Modified insulinotropic peptides are disclosed. The modified insulinotropic peptides are capable of forming a peptidase stabilized insulinotropic peptide. The modified insulinotropic peptides are capable of forming covalent bonds with one or more blood components to form a conjugate. The conjugates may be formed in vivo or ex vivo. The modified peptides are administered to treat humans with diabetes and other related diseases.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L149 ANSWER 11 OF 55 USPATFULL on STN
ACCESSION NUMBER: 2004:31832 USPATFULL
TITLE: Cyclic sulfamide derivatives and methods of use
INVENTOR(S): Coppola, Gary Mark, Budd Lake, NJ, UNITED STATES
Davies, John William, Montclair, NJ, UNITED STATES
Jewell, Charles Francis, Sudbury, MA, UNITED STATES
Li, Yu-Chin, Edison, NJ, UNITED STATES
Wareing, James Richard, Randolph, NJ, UNITED STATES
Sperbeck, Donald Mark, Berkeley Heights, NJ, UNITED STATES
Stams, Travis Matthew, Belle Mead, NJ, UNITED STATES
Topiol, Sidney Wolf, Fair Lawn, NJ, UNITED STATES
Vlattas, Isidoros, Summit, NJ, UNITED STATES

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 2004023974	A1	20040205
APPLICATION INFO.:	US 2003-405728	A1	20030402 (10)

	NUMBER	DATE
PRIORITY INFORMATION:	US 2002-369779P	20020403 (60)
	US 2002-369930P	20020403 (60)

DOCUMENT TYPE: Utility
FILE SEGMENT: APPLICATION
LEGAL REPRESENTATIVE: THOMAS HOXIE, NOVARTIS, CORPORATE INTELLECTUAL PROPERTY, ONE HEALTH PLAZA 430/2, EAST HANOVER, NJ, 07936-1080
NUMBER OF CLAIMS: 25
EXEMPLARY CLAIM: 1
LINE COUNT: 5806
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB Compounds of the formula ##STR1##

provide pharmacological agents which are inhibitors of PTPases, in particular, the compounds of formula I inhibit PTP-1B and TC PTP, and thus may be employed for the treatment of conditions associated with

PTPase activity. The compounds of the present invention may also be employed for inhibition of other enzymes with a phosphotyrosine binding region such as the SH2 domain. Accordingly, the compounds of formula I may be employed for prevention or treatment of insulin resistance associated with obesity, glucose intolerance, diabetes mellitus, hypertension and ischemic diseases of the large and small blood vessels. The compounds of the present invention may also be employed in the treatment, prevention or control of a number of conditions that accompany Type 2 diabetes, including hyperlipidemia, hypertriglyceridemia, atherosclerosis, vascular restenosis, irritable bowel syndrome, pancreatitis, adipose cell tumors and carcinomas such as liposarcoma, dyslipidemia, and other disorders where insulin resistance is indicated. In addition, the compounds of the present invention may be employed to treat or prevent cancer, osteoporosis, neurodegenerative and infectious diseases, and diseases involving inflammation and the immune system.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L149 ANSWER 12 OF 55 USPATFULL on STN
ACCESSION NUMBER: 2004:31729 USPATFULL
TITLE: Use of exendins and agonists thereof for the treatment of gestational diabetes mellitus
INVENTOR(S): Hiles, Richard A., San Diego, CA, UNITED STATES
Prickett, Kathryn S., San Diego, CA, UNITED STATES

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 2004023871	A1	20040205
APPLICATION INFO.:	US 2003-342014	A1	20030605 (10)

RELATED APPLN. INFO.: Continuation of Ser. No. US 1999-323867, filed on 1 Jun 1999, GRANTED, Pat. No. US 6506724
DOCUMENT TYPE: Utility
FILE SEGMENT: APPLICATION
LEGAL REPRESENTATIVE: ARNOLD & PORTER, IP DOCKETING DEPARTMENT, RM 1126(b), 555 12TH STREET, N.W., WASHINGTON, DC, 20004-1206
NUMBER OF CLAIMS: 17
EXEMPLARY CLAIM: 1
NUMBER OF DRAWINGS: 4 Drawing Page(s)
LINE COUNT: 4005
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB Methods for treating gestational diabetes which comprise administration of an effective amount of an exendin or an exendin agonist, alone or in conjunction with other compounds or compositions that lower blood glucose levels.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L149 ANSWER 13 OF 55 WPIDS COPYRIGHT 2004 THOMSON DERWENT on STN
ACCESSION NUMBER: 2004-480530 [45] WPIDS
DOC. NO. CPI: C2004-178703
TITLE: Treating or preventing diabetes or diabetes-related disease by **administering** exendin-4 compound and thiazolidinedione insulin sensitizer to patient.
DERWENT CLASS: A96 B04 D16
INVENTOR(S): KNUDSEN, L B
PATENT ASSIGNEE(S): (NOVO) NOVO NORDISK AS
COUNTRY COUNT: 106
PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG
WO 2004050115	A2	20040617	(200445)*	EN	31

RW: AT BE BG BW CH CY CZ DE DK EA EE ES FI FR GB GH GM GR HU IE IT KE LS LU MC MW MZ NL OA PT RO SD SE SI SK SL SZ TR TZ UG ZM ZW
W: AE AG AL AM AT AU AZ BA BB BG BR BW BY BZ CA CH CN CO CR CU CZ DE

DK DM DZ EC EE EG ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG
KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NI NO NZ OM
PG PH PL PT RO RU SC SD SE SG SK SL SY TJ TM TN TR TT TZ UA UG UZ
VC VN YU ZA ZM ZW

APPLICATION DETAILS:

PATENT NO	KIND	APPLICATION	DATE
WO 2004050115	A2	WO 2003-DK824	20031201

PRIORITY APPLN. INFO: US 2002-431999P 20021209; DK 2002-1864 20021203

AN 2004-480530 [45] WPIDS

AB WO2004050115 A UPAB: 20040716

NOVELTY - Treating or preventing (M1) diabetes or diabetes-related disease, involves **administering** exendin-4 compound and thiazolidinedione insulin sensitizer to the patient.

DETAILED DESCRIPTION - INDEPENDENT CLAIMS are also included for the following:

(1) use of exendin-4 compound and thiazolidinedione insulin sensitizer (I) for the preparation of one or more medicaments for carrying out (M1); and

(2) a **pharmaceutical composition** (II) comprising **exendin-4** compound and thiazolidinedione preservative.

ACTIVITY - Antidiabetic; Immunosuppressive; Cytostatic; Anorectic; Antilipemic; Hypotensive; Antiarteriosclerotic; Cardiovascular-Gen.; Ophthalmological; Nephrotropic; Neuroprotective.

MECHANISM OF ACTION - Stimulator of beta -cell proliferation. No supporting data is given.

USE - (M1) is useful for treating or preventing diabetes or diabetes related disease chosen from type 1 diabetes, type 2 diabetes, hyperglycemia, latent autoimmune diabetes in adults, maturity onset diabetes, polycystic ovarian syndrome, gestational diabetes, obesity, dyslipidemia, hyperlipidemia, hypertriglyceridemia, hyperlipoproteinemia, hypercholesterolemia, hypertension, arteriosclerosis, atherosclerosis, cardiovascular disease, diabetic retinopathy, background retinopathy, proliferative retinopathy, diabetic nephropathy, neuropathy and diabetic neuropathy, where the patient is human. (M1) is useful for increasing the number of beta -cells in patient. (I) is useful for the preparation of one or more medicaments for carrying out (M1). (II) is useful for carrying out (M1) (all claimed).

Dwg.0/0

L149 ANSWER 14 OF 55 IFIPAT COPYRIGHT 2004 IFI on STN DUPLICATE 9

AN 10343407 IFIPAT;IFIUDB;IFICDB

TITLE: EXENDINS, EXENDIN AGONISTS, AND METHODS FOR THEIR USE; USING EXENDRIN, OR ANTAGONIST THEREOF; APPETITE CONTROL

INVENTOR(S): Beeley; Nigel Robert Arnold, Solana Beach, CA, US
Bhavsar; Sunil, San Diego, CA, US
Prickett; Kathryn S., San Diego, CA, US

PATENT ASSIGNEE(S): Unassigned

AGENT: Lisa M. McGeehan Brobeck, Phleger & Harrison LLP, 12390 El Camino Real, San Diego, CA, 92130-2081, US

	NUMBER	PK	DATE
PATENT INFORMATION:	US 2003087821	A1	20030508
APPLICATION INFORMATION:	US 2002-187051		20020628

	APPLN. NUMBER	DATE	GRANTED PATENT NO. OR STATUS
CONTINUATION OF:	US 1998-3869	19980107	PENDING

	NUMBER	DATE
PRIORITY APPLN. INFO.:	US 1997-34905P	19970107 (Provisional)
	US 1997-55404P	19970808 (Provisional)
	US 1997-65442P	19971114 (Provisional)
	US 1997-66029P	19971114 (Provisional)
FAMILY INFORMATION:	US 2003087821	20030508
DOCUMENT TYPE:	Utility	
	Patent Application - First Publication	
FILE SEGMENT:	CHEMICAL	
	APPLICATION	

PARENT CASE DATA:

This application claims the benefit of U.S. Provisional Application No. 60/034,905, filed Jan. 7, 1997, U.S. Provisional Application No. 60/055,404, filed Aug. 8, 1997, U.S. Provisional Application No. 60/066,029, filed Nov. 14, 1997, and U.S. Provisional Application No. 60/065,442, November 14, 1997.

NUMBER OF CLAIMS: 31 10 Figure(s).

DESCRIPTION OF FIGURES:

FIG. 1 is a graphical depiction of the change of food intake in normal mice after intraperitoneal injection of exendin-4 and GLP-1.

FIG. 2 is a graphical depiction of the change of food intake in obese mice after intraperitoneal injection of exendin-4.

FIG. 3 is a graphical depiction of the change of food intake in rats after intracerebroventricular injection of exendin-4

FIG. 4 is a graphical depiction of the change of food intake in normal mice after intraperitoneal injection of exendin-4 (1-30) ("Compound 1").

FIG. 5 is a graphical depiction of the change of food intake in normal mice after intraperitoneal. injection of exendin-4 (1-30) amide ("Compound 2").

FIG. 6 is a graphical depiction of the change of food intake in normal mice after intraperitoneal injection of exendin-4 (1-28) amide ("Compound 3").

FIG. 7 is a graphical depiction of the change of food intake in normal mice after intraperitoneal injection of 14Leu, 25Phe exendin-4 amide ("Compound 4").

FIG. 8 is a graphical depiction of the change of food intake in normal mice after intraperitoneal injection of 4Leu, 25Phe exendin-4 (1-28) amide ("Compound 5").

FIG. 9 is a graphical depiction of the change of food intake in normal mice after intraperitoneal injection of 14Leu, 22Ala, 25Phe exendin-4 (1-28) amide ("Compound 6").

FIG. 10 depicts the amino acid sequences for certain exendin agonist compounds useful in the present invention (SEQ ID NOS 939).

AB Methods for treating conditions or disorders which can be alleviated by reducing food intake are disclosed which comprise administration of an effective amount of an exendin or an exendin agonist, alone or in conjunction with other compounds or compositions that affect satiety. The methods are useful for treating conditions or disorders, including obesity, Type II diabetes, eating disorders, and insulin-resistance syndrome. The methods are also useful for lowering the plasma glucose level, lowering the plasma lipid level, reducing the cardiac risk, reducing the appetite, and reducing the weight of subjects. Pharmaceutical compositions for use in the methods of the invention are also disclosed.

CLMN 31 10 Figure(s).

FIG. 1 is a graphical depiction of the change of food intake in normal mice after intraperitoneal injection of exendin-4 and GLP-1.

FIG. 2 is a graphical depiction of the change of food intake in obese mice after intraperitoneal injection of exendin-4.

FIG. 3 is a graphical depiction of the change of food intake in rats after intracerebroventricular injection of exendin-4

FIG. 4 is a graphical depiction of the change of food intake in normal mice after intraperitoneal injection of exendin-4 (1-30) ("Compound 1").

FIG. 5 is a graphical depiction of the change of food intake in normal mice after intraperitoneal. injection of exendin-4 (1-30) amide

("Compound 2").
FIG. 6 is a graphical depiction of the change of food intake in normal mice after intraperitoneal injection of exendin-4 (1-28) amide ("Compound 3").
FIG. 7 is a graphical depiction of the change of food intake in normal mice after intraperitoneal injection of 14Leu, 25Phe exendin-4 amide ("Compound 4").
FIG. 8 is a graphical depiction of the change of food intake in normal mice after intraperitoneal injection of 4Leu, 25Phe exendin-4 (1-28) amide ("Compound 5").
FIG. 9 is a graphical depiction of the change of food intake in normal mice after intraperitoneal injection of 14Leu, 22Ala, 25Phe exendin-4 (1-28) amide ("Compound 6").
FIG. 10 depicts the amino acid sequences for certain exendin agonist compounds useful in the present invention (SEQ ID NOS 939).

L149 ANSWER 15 OF 55 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2003:570838 CAPLUS
DOCUMENT NUMBER: 139:128032
TITLE: Combined use of a GLP-1 compound and another drug for treating dyslipidemia
INVENTOR(S): Knudsen, Lotte Bjerre; Selmer, Johan
PATENT ASSIGNEE(S): Novo Nordisk A/S, Den.
SOURCE: PCT Int. Appl., 20 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2003059378	A2	20030724	WO 2002-DK887	20021220
WO 2003059378	A3	20031127		

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, UZ, VC, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

US 2003143183	A1	20030731	US 2002-328284		20021223
PRIORITY APPLN. INFO.:			DK 2001-1970	A	20011229
			DK 2002-759	A	20020517
			US 2002-350088P	P	20020117

AB Methods and uses for treatment of dyslipidemia comprising administration of a GLP-1 compound and another antidyslipidemic drug.

L149 ANSWER 16 OF 55 USPATFULL on STN
ACCESSION NUMBER: 2003:300878 USPATFULL
TITLE: Treatment of diabetes and diabetic complications with NHE-1 inhibitors
INVENTOR(S): Tracey, W. Ross, Niantic, CT, UNITED STATES
Treadway, Judith L., Mystic, CT, UNITED STATES
PATENT ASSIGNEE(S): Pfizer Inc. (U.S. corporation)

	NUMBER	KIND	DATE	
PATENT INFORMATION:	US 2003212104	A1	20031113	
APPLICATION INFO.:	US 2003-428521	A1	20030501	(10)

NUMBER DATE

PRIORITY INFORMATION:	US 2002-380028P	20020502 (60)
DOCUMENT TYPE:	Utility	
FILE SEGMENT:	APPLICATION	
LEGAL REPRESENTATIVE:	PFIZER INC., PATENT DEPARTMENT, MS8260-1611, EASTERN POINT ROAD, GROTON, CT, 06340	
NUMBER OF CLAIMS:	18	
EXEMPLARY CLAIM:	1	
LINE COUNT:	2650	

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB This invention relates to methods of treating or preventing type 2 diabetes, diabetic neuropathy, diabetic cardiomyopathy, cataracts, diabetic retinopathy, foot ulcers, diabetic microangiopathy, diabetic macroangiopathy, diabetic ischemia reperfusion injury, diabetic cardiac ischemia reperfusion injury and/or insulin resistance syndrome (IRS) in mammals, particularly in humans, by **administering** a sodium-hydrogen exchanger type 1 (NHE-1) inhibitor or a pharmaceutical composition containing such an inhibitor. This invention also relates to combinations comprising NHE-1 inhibitors and a second pharmaceutical agent, said combinations being useful in treating type 2 diabetes, IRS, diabetic neuropathy, diabetic cardiomyopathy, cataracts, diabetic retinopathy, foot ulcers, diabetic ischemia reperfusion injury, diabetic cardiac ischemia reperfusion injury, diabetic microangiopathy and/or diabetic macroangiopathy.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L149 ANSWER 17 OF 55 USPATFULL on STN

ACCESSION NUMBER:	2003:207845 USPATFULL			
TITLE:	Combined use of a GLP-1 compound and modulator of diabetic late complications			
INVENTOR(S):	Knudsen, Lotte Bjerre, Valby, DENMARK Selmer, Johan, Farum, DENMARK			
	NUMBER	KIND	DATE	
PATENT INFORMATION:	US 2003144206	A1	20030731	
APPLICATION INFO.:	US 2002-328282	A1	20021223	(10)
	NUMBER		DATE	
PRIORITY INFORMATION:	DK 2001-1969		20011229	
	DK 2002-760		20020517	
	US 2002-350087P		20020117	(60)
DOCUMENT TYPE:	Utility			
FILE SEGMENT:	APPLICATION			
LEGAL REPRESENTATIVE:	Reza Green, Esq., Novo Nordisk Pharmaceuticals, Inc., 100 College Road West, Princeton, NJ, 08540			
NUMBER OF CLAIMS:	54			
EXEMPLARY CLAIM:	1			
LINE COUNT:	827			

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB Methods and uses for treatment of diabetic late complications comprising administration of a GLP-1 compound and a modulator of diabetic complications.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L149 ANSWER 18 OF 55 USPATFULL on STN

ACCESSION NUMBER:	2003:158954 USPATFULL
TITLE:	Long lasting synthetic glucagon-like peptide {GLP-1}
INVENTOR(S):	Bridon, Dominique P., Outremont, CANADA L'Archeveque, Benoit, Laval, CANADA Ezrin, Alan M., Moraga, CA, UNITED STATES Holmes, Darren L., Montreal, CANADA Leblanc, Anouk, Montreal, CANADA

St. Pierre, Serge, Ile Bizard, CANADA

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 2003108567	A1	20030612
APPLICATION INFO.:	US 2002-287892	A1	20021104 (10)

RELATED APPLN. INFO.: Division of Ser. No. US 2000-657332, filed on 7 Sep 2000, GRANTED, Pat. No. US 6514500

	NUMBER	DATE
PRIORITY INFORMATION:	US 1999-159783P	19991015 (60)

DOCUMENT TYPE: Utility
FILE SEGMENT: APPLICATION
LEGAL REPRESENTATIVE: Michael R. Ward, Morrison & Foerster LLP, 425 Market Street, San Francisco, CA, 94105-2482
NUMBER OF CLAIMS: 19
EXEMPLARY CLAIM: 1
LINE COUNT: 2359
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB Modified insulinotropic peptides are disclosed. The modified insulinotropic peptides are capable of forming a peptidase stabilized insulinotropic peptide. The modified insulinotropic peptides are capable of forming covalent bonds with one or more blood components to form a conjugate. The conjugates may be formed in vivo or ex vivo. The modified peptides are administered to treat humans with diabetes and other related diseases.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L149 ANSWER 19 OF 55 USPATFULL on STN
ACCESSION NUMBER: 2003:60207 USPATFULL
TITLE: Peptide agonists of GLP-1 activity
INVENTOR(S): Larsen, Bjarne Due, Br.o slashed.nsh.o slashed.j, DENMARK
Mikkelsen, Jens Damsgaard, Lyngby, DENMARK
Neve, S.o slashed.ren, Lyngby, DENMARK
PATENT ASSIGNEE(S): Zealand Pharma A/S, Glostrup, DENMARK (non-U.S. corporation)

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 6528486	B1	20030304
APPLICATION INFO.:	US 2000-614847		20000712 (9)

	NUMBER	DATE
PRIORITY INFORMATION:	US 1999-143591P	19990712 (60)

DOCUMENT TYPE: Utility
FILE SEGMENT: GRANTED
PRIMARY EXAMINER: Spector, Lorraine
ASSISTANT EXAMINER: Jiang, Dong
LEGAL REPRESENTATIVE: Buchanan, Robert L., Edwards & Angell, LLP
NUMBER OF CLAIMS: 2
EXEMPLARY CLAIM: 1
NUMBER OF DRAWINGS: 8 Drawing Figure(s); 8 Drawing Page(s)
LINE COUNT: 3573
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB The present invention relates to novel peptide conjugates which have increased stability and are useful in the treatment of excess levels of blood glucose.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L149 ANSWER 20 OF 55 USPATFULL on STN
ACCESSION NUMBER: 2003:33172 USPATFULL

TITLE: Long lasting synthetic glucagon like peptide {GLP-!}
INVENTOR(S): Bridon, Dominique P., Outremont, CANADA
L'Archeveque, Benoit, Laval, CANADA
Ezrin, Alan M., Moraga, CA, United States
Holmes, Darren L., Montreal, CANADA
Leblanc, Anouk, Montreal, CANADA
St. Pierre, Serge, Ile Bizard, CANADA
PATENT ASSIGNEE(S): Conjuchem, Inc., Montreal, CANADA (non-U.S. corporation)

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 6514500	B1	20030204
APPLICATION INFO.:	US 2000-657332		20000907 (9)

	NUMBER	DATE
PRIORITY INFORMATION:	US 1999-159783P	19991015 (60)

DOCUMENT TYPE: Utility
FILE SEGMENT: GRANTED
PRIMARY EXAMINER: Housel, James
ASSISTANT EXAMINER: Lucas, Zachariah
LEGAL REPRESENTATIVE: Morrison & Foerster LLP
NUMBER OF CLAIMS: 2
EXEMPLARY CLAIM: 1
NUMBER OF DRAWINGS: 0 Drawing Figure(s); 0 Drawing Page(s)
LINE COUNT: 2251
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB Modified insulinotropic peptides are disclosed. The modified insulinotropic peptides are capable of forming a peptidase stabilized insulinotropic peptide. The modified insulinotropic peptides are capable of forming covalent bonds with one or more blood components to form a conjugate. The conjugates may be formed in vivo or ex vivo. The modified peptides are administered to treat humans with diabetes and other related diseases.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L149 ANSWER 21 OF 55 USPAT2 on STN
ACCESSION NUMBER: 2003:165446 USPAT2
TITLE: Human glucose-dependent insulin-secreting cell line
INVENTOR(S): Perfetti, Riccardo, Los Angeles, CA, United States
PATENT ASSIGNEE(S): Cedars-Sinai Medical Center, Los Angeles, CA, United States (U.S. corporation)

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 6642003	B2	20031104
APPLICATION INFO.:	US 2001-920868		20010802 (9)

DOCUMENT TYPE: Utility
FILE SEGMENT: GRANTED
PRIMARY EXAMINER: Ketter, James
LEGAL REPRESENTATIVE: Pillsbury Winthrop LLP
NUMBER OF CLAIMS: 30
EXEMPLARY CLAIM: 1
NUMBER OF DRAWINGS: 11 Drawing Figure(s); 12 Drawing Page(s)
LINE COUNT: 1253
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB Disclosed herein is a novel cell line of human pancreatic cells that secrete insulin in a glucose-dependent manner. The cell line comprises pancreatic cells, such as PANC-1 cells, which are transfected so as to express IDX-1 and cultured in GLP-1. The cell line may be used to investigate the function and development of pancreatic cells, as well as to test the efficacy of drugs that stimulate insulin secretion.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L149 ANSWER 22 OF 55 WPIDS COPYRIGHT 2004 THOMSON DERWENT on STN
ACCESSION NUMBER: 2004-022543 [02] WPIDS
DOC. NO. CPI: C2004-007005
TITLE: Use of a glucagon like peptide-1 agonist or its salt for the preparation of a pharmaceutical composition for the treatment or prevention of an early cardiac or early cardiovascular disease in a diabetic or non-diabetic patient.
DERWENT CLASS: B04
INVENTOR(S): CARR, R D; CHRISTOFFERSEN, C; ELBROND, B; KNUDSEN, L B; LARSEN, J; NIELSEN, L B; ROLIN, B C; SELMER, J
PATENT ASSIGNEE(S): (CARR-I) CARR R D; (CHRI-I) CHRISTOFFERSEN C; (ELBR-I) ELBROND B; (KNUD-I) KNUDSEN L B; (LARS-I) LARSEN J; (NIEL-I) NIELSEN L B; (ROLI-I) ROLIN B C; (SELM-I) SELMER J; (NOVO) NOVO NORDISK AS
COUNTRY COUNT: 103
PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG
WO 2003084563	A1	20031016	(200402)*	EN	14
RW: AT BE BG CH CY CZ DE DK EA EE ES FI FR GB GH GM GR HU IE IT KE LS LU MC MW MZ NL OA PT RO SD SE SI SK SL SZ TR TZ UG ZM ZW					
W: AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH CN CO CR CU CZ DE DK DM DZ EC EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NI NO NZ OM PH PL PT RO RU SC SD SE SG SK SL TJ TM TN TR TT TZ UA UG UZ VC VN YU ZA ZM ZW					
US 2003220255	A1	20031127	(200402)		
AU 2003226913	A1	20031020	(200436)		

APPLICATION DETAILS:

PATENT NO	KIND	APPLICATION	DATE
WO 2003084563	A1	WO 2003-DK216	20030402
US 2003220255	A1 Provisional	US 2002-375255P	20020423
		US 2003-406426	20030403
AU 2003226913	A1	AU 2003-226913	20030402

FILING DETAILS:

PATENT NO	KIND	PATENT NO
AU 2003226913	A1 Based on	WO 2003084563

PRIORITY APPLN. INFO: US 2002-375255P 20020423; DK 2002-499 20020404; US 2003-406426 20030403
AN 2004-022543 [02] WPIDS
AB WO2003084563 A UPAB: 20040107
NOVELTY - In the treatment or prevention of an early cardiac or early cardiovascular disease in a diabetic or non-diabetic patient a glucagon like peptide-1 (GLP1) agonist or its salt is used.
ACTIVITY - Cardiant; Cardiovascular-Gen.; Antiarrhythmic; Antianginal; Antiarteriosclerotic; Vasotropic; Hypotensive.
MECHANISM OF ACTION - Glucose metabolism regulator; Cardiovascular hemodynamics regulator; Brain natriuretic peptide (BNP) in plasma and/or heart tissue inhibitor. Hearts from 12 streptozotocin (STZ)-treated pigs were collected. The pigs were treated with STZ 2 weeks prior to dosing with either the GLP-1 derivative, Arg34, Lys26(N- eta (gamma -Glu(N-alpha -hexadecanoyl)))-GLP-1(7-37) (NN2211) for 4 weeks, at a dose of 3.3 micro g/kg, subcutaneously once daily or with a vehicle. STZ-treated pigs were either hyperglycemic or glucose intolerant and had impaired insulin secretion upon oral glucose tolerance tests. BNP mRNA and protein levels

in cardiac biopsies were measured with real-time PCR and RIA assays, respectively. BNP mRNA levels were normalized by beta -actin mRNA levels. BNP mRNA levels were similar in right atrial (RA), left atrial (LA) and in left ventricular (LV) biopsies from vehicle treated diabetic pigs (-GLP). However, in hearts from NN2211 (+GLP) treated pigs the levels of BNP were significantly lower than in vehicle treated pigs. The BNP mRNAs (arb.units) in the RA, LA and LV in the NN2211/vehicle treated pigs was found to be 0.13/1.3, 0.37/1.5 and 0.75/1.15, respectively.

USE - For the treatment or prevention of an early cardiac or early cardiovascular disease (e.g. left ventricular hypertrophy, coronary artery disease, essential hypertension, acute hypertensive emergency, cardiomyopathy, heart insufficiency, exercise tolerance, chronic heart failure, arrhythmia, cardiac dysrhythmia, syncopy, atherosclerosis, mild chronic heart failure, angina pectoris, cardiac bypass reocclusion, intermittent claudication (e.g. atherosclerosis obliterens), diastolic dysfunction and systolic dysfunction) in a diabetic or non-diabetic patient; for the preparation of a pharmaceutical composition for reducing the level of brain natriuretic peptide (BNP) in plasma and/or heart tissue in a diabetic or non-diabetic patient (all claimed). Also useful for the treatment of myocardial infarction, acute coronary syndrome, unstable angina, non-Q-wave cardiac necrosis, Q-wave myocardial infarct and morbidity after stroke.

ADVANTAGE - The GLP-1 agonists are in the form of stable derivatives and exhibit a protracted profile of action compared to the corresponding other GLP-1 analogs. The GLP-1 analogs lower the brain natriuretic peptide (BNP) in the plasma and/or heart tissue, in addition to lowering blood glucose and plasma lipids.

Dwg.0/1

L149 ANSWER 23 OF 55 CAPLUS COPYRIGHT 2004 ACS on STN

ACCESSION NUMBER: 2003:995007 CAPLUS

DOCUMENT NUMBER: 140:175481

TITLE: Antagonism of rat β-cell voltage-dependent K+ currents by exendin 4 requires dual activation of the cAMP/protein kinase A and phosphatidylinositol 3-kinase signaling pathways

AUTHOR(S): MacDonald, Patrick E.; Wang, Xiaolin; Xia, Fuzhen; El-kholy, Wasim; Targonsky, Elisha D.; Tsushima, Robert G.; Wheeler, Michael B.

CORPORATE SOURCE: Department of Physiology, University of Toronto, Toronto, ON, M1H 1E6, Can.

SOURCE: Journal of Biological Chemistry (2003), 278(52), 52446-52453
CODEN: JBCHA3; ISSN: 0021-9258

PUBLISHER: American Society for Biochemistry and Molecular Biology

DOCUMENT TYPE: Journal

LANGUAGE: English

AB Antagonism of voltage-dependent K+ (Kv) currents in pancreatic β-cells may contribute to the ability of glucagon-like peptide-1 (GLP-1) to stimulate insulin secretion. The mechanism and signaling pathway regulating these currents in rat β-cells were investigated using the GLP-1 receptor agonist exendin 4. Inhibition of Kv currents resulted from a 20-mV leftward shift in the voltage dependence of steady-state inactivation. Blocking cAMP or protein kinase A (PKA) signaling (Rp-cAMP and H-89, resp.) prevented the inhibition of currents by exendin 4. However, direct activation of this pathway alone by intracellular dialysis of cAMP or the PKA catalytic subunit (cPKA) could not inhibit currents, implicating a role for alternative signaling pathways. A number of phosphorylation sites associated with phosphatidylinositol 3 (PI3)-kinase activation were up-regulated in GLP-1-treated MIN6 insulinoma cells, and the PI3 kinase inhibitor wortmannin could prevent antagonism of β-cell currents by exendin 4. Antagonists of Src family kinases (PP1) and the epidermal growth factor (EGF) receptor (AG1478) also prevented current inhibition by exendin 4, demonstrating a role for Src kinase-mediated transactivation of the EGF

tyrosine kinase receptor. Accordingly, the EGF receptor agonist betacellulin could replicate the effects of exendin 4 in the presence of elevated intracellular cAMP. Downstream, the PKCζ pseudosubstrate inhibitor could prevent current inhibition by exendin 4. Therefore, antagonism of β-cell Kv currents by GLP-1 receptor activation requires both cAMP/PKA and PI3 kinase/PKCζ signaling via transactivation of the EGF receptor. This represents a novel dual pathway for the control of Kv currents by G protein-coupled receptors.

REFERENCE COUNT: 51 THERE ARE 51 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L149 ANSWER 24 OF 55 CAPLUS COPYRIGHT 2004 ACS on STN DUPLICATE 10

ACCESSION NUMBER: 2003:677779 CAPLUS
DOCUMENT NUMBER: 139:270776
TITLE: Effect on glycemic control of exenatide (synthetic exendin-4) additive to existing metformin and/or sulfonylurea treatment in patients with type 2 diabetes
AUTHOR(S): Fineman, Mark S.; Bicsak, Thomas A.; Shen, Larry Z.; Taylor, Kristin; Gaines, Eling; Varns, Amanda; Kim, Dennis; Baron, Alain D.
CORPORATE SOURCE: Amylin Pharmaceuticals, Inc., San Diego, CA, USA
SOURCE: Diabetes Care (2003), 26(8), 2370-2377
CODEN: DICAD2; ISSN: 0149-5992
PUBLISHER: American Diabetes Association, Inc.
DOCUMENT TYPE: Journal
LANGUAGE: English

AB AC2993 (synthetic exendin-4; exenatide) is a peptide that enhances glucose-dependent insulin secretion, suppresses inappropriately elevated glucagon secretion, and slows gastric emptying. AC2993 also promotes β-cell proliferation and neogenesis in vitro and in animal models. This study examines the activity and safety of s.c. injected AC2993 in patients with type 2 diabetes currently treated with diet and/or oral antidiabetic agents (OAAs). A total of 109 patients treated with diet and a sulfonylurea and/or metformin were enrolled in a blinded study. Patients were randomly assigned to one of three s.c. (SC) injected regimens of AC2993 (0.08 μg/kg) or placebo for 28 days. All three AC2993 regimens led to significant redns. in serum fructosamine relative to placebo ($P \leq 0.004$). Mean redns. ranged from 39 to 46 μmol/l. All AC2993 groups had redns. in HbA1c ranging from 0.7 to 1.1% ($P \leq 0.006$). An end-of-study HbA1c <7% was achieved by 15% of AC2993 patients vs. 4% of placebo patients, confirming AC2993 effects on fasting and postprandial glycemia. On days 14 and 28, the β-cell index (homeostasis model assessment) for patients treated with AC2993 was 50-100% higher than baseline, contrasting with unchanged levels for placebo. The most common adverse event was transient mild-to-moderate nausea. AC2993 is a promising therapeutic for patients with type 2 diabetes. In this study, it had significant effects on HbA1c levels in patients not currently achieving optimal glucose control with diet and/or OAAs.

REFERENCE COUNT: 37 THERE ARE 37 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L149 ANSWER 25 OF 55 CAPLUS COPYRIGHT 2004 ACS on STN DUPLICATE 11

ACCESSION NUMBER: 2003:496771 CAPLUS
DOCUMENT NUMBER: 139:159323
TITLE: Pharmacology of exenatide (synthetic exendin-4) for the treatment of type 2 diabetes
AUTHOR(S): Nielsen, Loretta L.; Baron, Alain D.
CORPORATE SOURCE: Amylin Pharmaceuticals Inc, San Diego, CA, 92121, USA
SOURCE: Current Opinion in Investigational Drugs (Thomson Current Drugs) (2003), 4(4), 401-405
CODEN: COIDAZ; ISSN: 1472-4472
PUBLISHER: Thomson Current Drugs
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English

AB A review. New therapies for the long-term treatment of type 2 diabetes are needed to ameliorate declining pancreatic β-cell function. Ideally, these therapies should lower fasting and post-prandial blood glucose, produce no hypoglycemia or weight gain, cause no other limiting side effects, and reduce cardiovascular complications. Exenatide (synthetic exendin-4) is a potential therapeutic which may fulfill these criteria. Dose-ranging studies have identified an optimal dose of 0.05 to 0.2 μg/kg administered s.c. twice daily. Pharmacokinetic data support a pivotal study design which mitigates the transient nausea observed in early studies by including a dose initiation period of 3 mo at 5 μg twice daily, followed by maintenance therapy at 10 μg twice daily. Ongoing studies suggest exenatide improves glycemic control through a combination of mechanisms discussed in this review.
REFERENCE COUNT: 56 THERE ARE 56 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L149 ANSWER 26 OF 55 SCISEARCH COPYRIGHT 2004 THOMSON ISI on STN
ACCESSION NUMBER: 2003:910274 SCISEARCH
THE GENUINE ARTICLE: 683WJ
TITLE: Synthetic **exendin4** (exenatide) modulates beta cell mass in insulin resistant fa/fa rats
AUTHOR: Nikoulina S (Reprint); Gedulin B; Gedulin G; Putvinski S; Young A; Baron A; Parkes D
SOURCE: DIABETES, (JUN 2003) Vol. 52, Supp. [1], pp. A366-A366. Publisher: AMER DIABETES ASSOC, 1701 N BEAUREGARD ST, ALEXANDRIA, VA 22311-1717 USA. ISSN: 0012-1797.
DOCUMENT TYPE: Conference; Journal
LANGUAGE: English
REFERENCE COUNT: 0

L149 ANSWER 27 OF 55 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2003:643746 CAPLUS
DOCUMENT NUMBER: 139:359047
TITLE: Exendin-4, a GLP-1 receptor agonist, stimulates pituitary-adrenocortical axis in the rat: investigations into the mechanism(s) underlying Ex4 effect
AUTHOR(S): Malendowicz, Ludwik K.; Nussdorfer, Gastone G.; Nowak, Krzysztof W.; Ziolkowska, Agnieszka; Tortorella, Cinzia; Trejter, Marcin
CORPORATE SOURCE: Department of Histology and Embryology, Karol Marcinkowski University of Medical Sciences, Poznan, PL-60781, Pol.
SOURCE: International Journal of Molecular Medicine (2003), 12(2), 237-241 CODEN: IJMMFG; ISSN: 1107-3756
PUBLISHER: International Journal of Molecular Medicine
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Exendin-4 (Ex4) is a potent and long-lasting agonist of glucagon-like peptide-1 (GLP-1), which has been previously found to stimulate pituitary-adrenal axis in the rat. The aims of the present study was to gain insight into the mechanism(s) involved in the Ex4-induced rise in the rat plasma concns. of ACTH, aldosterone and corticosterone. Preliminary time- and dose-response studies showed that the maximum stimulating effect of Ex4 occurred within 1 or 2 h and at dose ranging from 0.5 to 2.0 nmol/100 g body weight The GLP-1 receptor (GLP-1R) antagonist Ex(9-39) did not significantly affect ACTH, aldosterone and corticosterone responses to Ex4. Neither the administration of CRH and arginine vasopressin (AVP)-receptor antagonists nor adrenal demodulation prevented pituitary-adrenal axis responses to Ex4. The prolonged (4 or 6 days) suppression of the pituitary ACTH release by dexamethasone impaired corticosterone, but not aldosterone response to Ex4. The following conclusions are drawn: (i) Ex4 stimulates rat pituitary-adrenal axis through receptors other than the classic GLP-1R; (ii) neither CRH and AVP

nor medullary catecholamines are involved in the Ex4-induced stimulation of ACTH release; (iii) ACTH stimulation accounts for the rise in corticosterone plasma concentration; and (iv) the aldosterone secretagogue effect of Ex4 occurs via a mechanism independent of the stimulation of either ACTH or medullary catecholamines.

REFERENCE COUNT: 28 THERE ARE 28 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L149 ANSWER 28 OF 55 CAPLUS COPYRIGHT 2004 ACS on STN

ACCESSION NUMBER: 2003:415690 CAPLUS
DOCUMENT NUMBER: 139:208036
TITLE: Interrelationship among insulin, glucagon and somatostatin secretory responses to exendin-4 in the perfused rat pancreas
AUTHOR(S): Silvestre, Ramona A.; Rodriguez-Gallardo, Jovita; Egido, Eva M.; Marco, J.
CORPORATE SOURCE: Hospital Universitario Clinica Puerta de Hierro and Department of Physiology, Universidad Autonoma de Madrid, Madrid, 28035, Spain
SOURCE: European Journal of Pharmacology (2003), 469(1-3), 195-200
CODEN: EJPHAZ; ISSN: 0014-2999
PUBLISHER: Elsevier Science B.V.
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The authors have investigated the effect of exendin-4 on insulin, glucagon and somatostatin output in the perfused rat pancreas. At 9 mM glucose, exendin-4 potentiated the insulin and somatostatin responses to arginine and reduced the glucagon response to this amino acid. Thus, this reduction might be thought to be paracrine-mediated through the concomitant increase in insulin and somatostatin concns. At 3.2 mM glucose, exendin-4 did not affect insulin secretion, reduced glucagon release and stimulated somatostatin output. Furthermore, exendin-4 reduced glucagon secretion as induced by a glucose decline (from 11 to 3.2 mM) without affecting insulin or somatostatin responses. In summary, exendin-4 stimulated insulin and somatostatin secretion and reduced glucagon release. The glucagonostatic effect of exendin-4 was observed under conditions in which insulin and somatostatin were not affected, thus indicating that exendin-4, per se, inhibits A-cell secretion. Indeed, an addnl. glucagonostatic effect of exendin-4, mediated by its stimulation of insulin and/or somatostatin secretion, cannot be ruled out.

REFERENCE COUNT: 34 THERE ARE 34 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L149 ANSWER 29 OF 55 IFIPAT COPYRIGHT 2004 IFI on STN DUPLICATE 12

AN 10193961 IFIPAT;IFIUDB;IFICDB
TITLE: USE OF EXENDINS AND AGONISTS THEREOF FOR THE REDUCTION OF FOOD INTAKE; OBESITY, ANTIDIABETIC AGENTS FOR TYPE II DIABETES, EATING DISORDERS, AND INSULIN-RESISTANCE SYNDRONE; ANTILIPOLYTIC AGENTS; (EXTENDINS ARE PEPTIDES FOUND IN THE VENOM OF THE ARIZONA GILA MONSTER)
INVENTOR(S): BEELEY; NIGEL ROBERT ARNOLD, SOLANA BEACH, CA, US
BHAVSAR; SUNIL, SAN DIEGO, CA, US
PRICKETT; KATHRYN S., SAN DIEGO, CA, US
PATENT ASSIGNEE(S): Unassigned
AGENT: LYON & LYON LLP, 633 WEST FIFTH STREET, SUITE 4700, LOS ANGELES, CA, 90071, US

	NUMBER	PK	DATE
PATENT INFORMATION:	US 2002137666	A1	20020926
APPLICATION INFORMATION:	US 1998-3869		19980107

NUMBER	DATE

PRIORITY APPLN. INFO.: US 1997-34905P 19970107 (Provisional)
US 1997-55404P 19970808 (Provisional)
US 1997-65442P 19971114 (Provisional)
US 1997-66029P 19971114 (Provisional)
FAMILY INFORMATION: US 2002137666 20020926
DOCUMENT TYPE: Utility
Patent Application - First Publication
FILE SEGMENT: CHEMICAL
APPLICATION

NUMBER OF CLAIMS: 31 10 Figure(s).
DESCRIPTION OF FIGURES:
FIG. 1 is a graphical depiction of the change of food intake in normal mice after intraperitoneal injection of exendin-4 and GLP-1.
FIG. 2 is a graphical depiction of the change of food intake in obese mice after intraperitoneal injection of exendin-4.
FIG. 3 is a graphical depiction of the change of food intake in rats after intracerebroventricular injection of exendin-4
FIG. 4 is a graphical depiction of the change of food intake in normal mice after intraperitoneal injection of exendin-4 (1-30) ("Compound 1").
FIG. 5 is a graphical depiction of the change of food intake in normal mice after intraperitoneal injection of exendin-4 (1-30) amide ("Compound 2").
FIG. 6 is a graphical depiction of the change of food intake in normal mice after intraperitoneal injection of exendin-4 (1-28) amide ("Compound 3").
FIG. 7 is a graphical depiction of the change of food intake in normal mice after intraperitoneal injection of 4Leu, 25Phe exendin-4 amide ("Compound 41").
FIG. 8 is a graphical depiction of the change of food intake in normal mice after intraperitoneal injection of 4Leu, 25Phe exendin-4 (1-28) amide ("Compound 5").
FIG. 9 is a graphical depiction of the change of food intake in normal mice after intraperitoneal injection of 14Leu, 22Ala, 25Phe exendin-4 (1-28) amide ("Compound 6").
FIG. 10 depicts the amino acid sequences for certain exendin agonist compounds useful in the present invention (SEQ ID NOS 939).

AB Methods for treating conditions or disorders which can be alleviated by reducing food intake are disclosed which comprise administration of an effective amount of an exendin or an exendin agonist, alone or in conjunction with other compounds or compositions that affect satiety. The methods are useful for treating conditions or disorders, including obesity, Type II diabetes, eating disorders, and insulin-resistance syndrome. The methods are also useful for lowering the plasma glucose level, lowering the plasma lipid level, reducing the cardiac risk, reducing the appetite, and reducing the weight of subjects. Pharmaceutical compositions for use in the methods of the invention are also disclosed.

CLMN 31 10 Figure(s).
FIG. 1 is a graphical depiction of the change of food intake in normal mice after intraperitoneal injection of exendin-4 and GLP-1.
FIG. 2 is a graphical depiction of the change of food intake in obese mice after intraperitoneal injection of exendin-4.
FIG. 3 is a graphical depiction of the change of food intake in rats after intracerebroventricular injection of exendin-4
FIG. 4 is a graphical depiction of the change of food intake in normal mice after intraperitoneal injection of exendin-4 (1-30) ("Compound 1").
FIG. 5 is a graphical depiction of the change of food intake in normal mice after intraperitoneal injection of exendin-4 (1-30) amide ("Compound 2").
FIG. 6 is a graphical depiction of the change of food intake in normal mice after intraperitoneal injection of exendin-4 (1-28) amide ("Compound 3").
FIG. 7 is a graphical depiction of the change of food intake in normal mice after intraperitoneal injection of 4Leu, 25Phe exendin-4 amide ("Compound 41").
FIG. 8 is a graphical depiction of the change of food intake in normal mice after intraperitoneal injection of 4Leu, 25Phe exendin-4 (1-28) amide ("Compound 5").

FIG. 9 is a graphical depiction of the change of food intake in normal mice after intraperitoneal injection of 14Leu, 22Ala, 25Phe exendin-4 (1-28) amide ("Compound 6").

FIG. 10 depicts the amino acid sequences for certain exendin agonist compounds useful in the present invention (SEQ ID NOS 939).

L149 ANSWER 30 OF 55 IFIPAT COPYRIGHT 2004 IFI on STN DUPLICATE 13

AN 10105567 IFIPAT;IFIUDB;IFICDB

TITLE: LONG LASTING INSULINOPTROPIC PEPTIDES; MODIFIED PEPTIDES CAPABLE OF FORMING COVALENT BONDS WITH ONE OR MORE BLOOD COMPONENTS, ESPECIALLY ALBUMIN, TO FORM A CONJUGATE; ADMINISTERED TO TREAT HUMANS WITH DIABETES

INVENTOR(S): Bridon; Dominique P., Outremont, CA
Ezrin; Alan M., Moraga, CA, US
Holmes; Darren L., Montreal, CA
L'Archeveque; Benoit, Leval, CA
Leblanc; Anouk, Montreal, CA
St. Pierre; Serge, Ile Bizard, CA

PATENT ASSIGNEE(S): Unassigned

PATENT ASSIGNEE PROBABLE: ConjuChem Inc CA (Probable)

AGENT: Michael R. Ward Morrison & Foerster LLP, 425 Market Street, San Francisco, CA, 94105-2482, US

	NUMBER	PK	DATE
PATENT INFORMATION:	US 2002049153	A1	20020425
APPLICATION INFORMATION:	US 2001-876388		20010606

	APPLN. NUMBER	DATE	GRANTED PATENT NO. OR STATUS
Section 371 PCT Filing OF:	WO 2000-US13563	20000517	UNKNOWN
DIVISION OF:	US 2000-623618	20000905	PENDING

	NUMBER	DATE	
PRIORITY APPLN. INFO.:	US 1999-134406P	19990517	(Provisional)
	US 1999-159783P	19991015	(Provisional)
FAMILY INFORMATION:	US 2002049153	20020425	
	US 6593295	20030715	

DOCUMENT TYPE: Utility
Patent Application - First Publication

FILE SEGMENT: CHEMICAL
APPLICATION

NUMBER OF CLAIMS: 19

AB Modified insulinotropic peptides are disclosed. The modified insulinotropic peptides are capable of forming a peptidase stabilized insulinotropic peptide. The modified insulinotropic peptides are capable of forming covalent bonds with one or more blood components to form a conjugate. The conjugates may be formed in vivo or ex vivo. The modified peptides are administered to treat humans with diabetes and other related diseases.

CLMN 19

L149 ANSWER 31 OF 55 CAPLUS COPYRIGHT 2004 ACS on STN

ACCESSION NUMBER: 2003:860512 CAPLUS

DOCUMENT NUMBER: 139:302007

TITLE: Method for determining activity of insulin secretion-promoting peptide

INVENTOR(S): Sun, Yukun; Wu, Dengxi; Yu, Gang; Zhou, Jiaxiang

PATENT ASSIGNEE(S): Shanghai Huayi Biotechnology Co., Ltd., Peop. Rep. China

SOURCE: Faming Zhuanli Shenqing Gongkai Shuomingshu, 11 pp.
CODEN: CNXXEV

DOCUMENT TYPE: Patent
LANGUAGE: Chinese
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
CN 1363838	A	20020814	CN 2001-126695	20010907
CN 1131433	B	20031217		
PRIORITY APPLN. INFO.:			CN 2001-126695	20010907

AB The activity of insulin secretion-promoting peptide (such as **exendin4** or glucagon like peptide-1) is determined by injecting insulin secretion-promoting peptide into C57/BL/6J mouse and then determining the secretion of insulin and hypoglycemic effect.

L149 ANSWER 32 OF 55 USPATFULL on STN
ACCESSION NUMBER: 2002:239150 USPATFULL
TITLE: Method of acylating peptides and novel acylating agents
INVENTOR(S): Hansen, Louis Brammer, V.ae butted.rl.o slashed.se, DENMARK
PATENT ASSIGNEE(S): Novo Nordisk A/S, Bagsvaerd, DENMARK (non-U.S. corporation)

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 6451974	B1	20020917
APPLICATION INFO.:	US 2000-523783		20000313 (9)

	NUMBER	DATE
PRIORITY INFORMATION:	EP 1999-610019	19990317
	US 1999-126882P	19990330 (60)

DOCUMENT TYPE: Utility
FILE SEGMENT: GRANTED
PRIMARY EXAMINER: Low, Christopher S. F.
ASSISTANT EXAMINER: Mohamed, Abdel A.
LEGAL REPRESENTATIVE: Green, Esq., Rezo, Bork, Esq., Richard W.
NUMBER OF CLAIMS: 17
EXEMPLARY CLAIM: 1
NUMBER OF DRAWINGS: 0 Drawing Figure(s); 0 Drawing Page(s)
LINE COUNT: 708
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB Provided is a method for acylating one or more amino groups of a peptide or protein such as GLP-1. This method includes (a) reacting a peptide or protein having at least one free amino group with an acylating agent of formula I ##STR1##

wherein n is 0-8; R.sup.1 is COOR.sup.4; R.sup.2 is a lipophilic moiety; R.sup.3 and its attached carboxyl group designate a reactive ester or a reactive N-hydroxy imide ester; and R.sup.4 is selected from hydrogen, C.sub.1-12-alkyl and benzyl, under basic conditions in a mixture of an aprotic polar solvent and water; and (b) if R.sup.4 is not hydrogen, saponifying the acylated peptide or protein ester group under basic conditions in order to obtain an N-acylated peptide or an N-acylated protein.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L149 ANSWER 33 OF 55 BIOTECHDS COPYRIGHT 2004 THOMSON DERWENT/ISI on STN
ACCESSION NUMBER: 2003-05805 BIOTECHDS
TITLE: Novel heterologous fusion protein, useful for treating non-insulin dependent diabetes mellitus or obesity, comprises a glucagon-like peptide 1 compound fused to human albumin or to the Fc portion of an immunoglobulin;
vector-mediated gene transfer and expression in host cell for recombinant protein production and disease therapy

AUTHOR: GLAESNER W; MICANOVIC R; TSCHANG S R
PATENT ASSIGNEE: LILLY and CO ELI
PATENT INFO: WO 2002046227 13 Jun 2002
APPLICATION INFO: WO 2001-US43165 29 Nov 2001
PRIORITY INFO: US 2000-251954 7 Dec 2000; US 2000-251954 7 Dec 2000
DOCUMENT TYPE: Patent
LANGUAGE: English
OTHER SOURCE: WPI: 2003-018534 [01]
AN 2003-05805 BIOTECHDS
AB DERWENT ABSTRACT:

NOVELTY - A heterologous fusion protein (I) comprising a first polypeptide (P1) fused to a second polypeptide (P2), where P1 or P2 has a N-terminus and a C-terminus, and P1 is a glucagon-like peptide 1 (GLP-1) compound and P2 is a human albumin or its analog or fragment, or the Fc portion of an immunoglobulin or its analog or fragment, where the C-terminus of P1 is fused to the N-terminus of P2, is new.

DETAILED DESCRIPTION - INDEPENDENT CLAIMS are also included for the following: (1) a polynucleotide (II) encoding (I); (2) a vector (III) comprising (II); (3) a host cell (IV) comprising (III) or expressing (I); (4) production of (I); and (5) a **pharmaceutical formulation** (V) adapted for the treatment of patients with non-insulin dependent diabetes mellitus comprising (I).

BIOTECHNOLOGY - Preparation: (I) is produced by transcribing and translating (II) under conditions, where (I) is expressed in detectable amounts (claimed). Preferred Peptide: In (I), the C-terminus of P1 is fused to the N-terminus of P2 by a peptide linker selected from a glycine rich peptide, and a peptide having a sequence (GGGGS)n, where n is 1,2,3,4,5 or 6, preferably 3. The GLP-1 compound comprises the sequence of A1, A2, A3, A4, A5 or A6: X1-X2-X3-G-X4-X5-T-S-D-X6-S-X7-Y-L-E-X8-X9-X10-A-X11-X12-F-I-X13-X14-L-X15-X16-X17-X18-X19 (A1); X1-X2-E-G-X4-X5-T-S-D-X20-S-S-Y-L-E-X8-X21-X22-A-X23-X12-F-I-A-X13-L-X15-X16-X17-X24-X19 (A2); X1-X2-E-G-T-X5-T-S-D-X20-S-S-Y-L-E-X8-X21-A-A-X23-E-F-I-X13-W-L-V-K-X17-R-X25 (A3); X1-X2-E-G-T-F-T-S-D-V-S-S-Y-L-E-X8-X21-A-A-K-X12-F-I-X13-W-L-V-K-G-R-X19 (A4); X1-X26-E-G-T-F-T-S-D-X27-S-X28-X29-X30-E-X31-X31-A-X32-X33-X34-F-I-X35-W-L-X36-X37-G-X38-X39 (A5); X1-X2-E-G-T-X40-T-S-D-X41-S-X42-X43-X44-E-X45-Q-A-X46-K-X47-F-I-X35-W-L-X48-K-G-R-X49 (A6). where X1 = L-His, D-His, desamino-His, 2-amino-histidine, beta-hydroxy-histidine, homohistidine, alpha-fluoromethyl-histidine, or alpha-methyl-histidine; X2 = Gly (preferred), Ala, Val, Leu, Ile, Ser or Thr; X3 = Thr, Ser, Arg, Lys, Trp, Phe, Tyr, Glu or His; X4 = Asp, Glu, Arg, Thr, Ala, Lys or His; X5 = His, Trp, Phe or Tyr; X6 = Leu, Ser, Thr, Trp, His, Phe, Asp, Val, Tyr, Glu, or Ala; X7 = His, Pro, Asp, Glu, Arg, Ser, Ala or Lys; X8 = Gly, Asp, Glu, Gln, Asn, Lys, Arg, or Cys; X9 = His, Asp, Lys, Glu, Gln, or Arg; X10 = Glu, Arg, Ala or Lys; X11 = Trp, Tyr, Phe, Asp, Lys, Glu or His; X12 = Ala, Glu, His, Phe, Tyr, Trp, Arg or Lys; X13 = Ala, Glu, Asp, Ser or His; X14 = Asp, Glu, Ser, Thr, Arg, Trp or Lys; X15 = Asp, Arg, Val, Lys, Ala, Gly, or Glu; X16 = Glu, Lys or Asp; X17 = Thr, Ser, Lys, Arg, Trp, Tyr, Phe, Asp, Gly, Pro, His or Glu; X18 = Thr, Ser, Asp, Trp, Tyr, Phe, Arg, Glu or His; X19 = Lys, Arg, Thr, Ser, Glu, Asp, Trp, Tyr, Phe, His, Gly, Gly-Pro, or is absent; X20 = Leu, Ser, Thr, Trp, His, Phe, Asp, Val, Glu or Ala. X21 = His, Asp, Lys, Glu or Gln; X22 = Glu, His, Ala, Lys; X23 = Asp, Lys, Glu, or His; X24 = Arg, Glu or His; X25 = X19, -NH2 or Gly-Pro-NH2; X26 = Gly (preferred), Ala or Val; X27 = Leu or Val; X28 = Lys or Ser; X29 = Gln or Tyr; X30 = Met or Leu; X31 = Glu or Gln; X32 = Val or Ala; X33 = Arg or Lys; X34 = Leu or Glu; X35 = Glu or Ala; X36 = Val or Lys; X37 = Asn or Lys; X38 = Gly or Arg; X39 = Gly, Pro, Pro-Ser-Ser-Gly-Ala-Pro-Pro-Pro-Ser, or is absent; X40 = Phe, Trp or Tyr; X41 = Val, Trp, Ile, Leu, Phe or Tyr; X42 = Ser, Trp, Tyr, Phe, Lys, Ile, Leu, Val; X43 = Tyr, Trp or Phe; X44 = Leu, Phe, Tyr or Trp; X45 = Gly, Glu, Asp or Lys; X46 = Ala, Val, Ile or Leu; X47 = Glu, Ile or Ala; X48 = Val or Ile; X49 = Gly, His, NH2 or is absent. The GLP-1 compound has no more than 6 amino acids, preferably no more than 2 amino acids, that differ from the corresponding amino acid in GLP-1(7-37)OH, GLP-1 (7-36)OH or **Exendin-4**. In A4, X2 is Gly or Val, and X13 is Ala, Glu (most preferred), Asp, Ser or His. Alternatively, X2 is

Gly or Val, and X19 is His (preferred), Phe, Tyr, Trp, Asp, Glu, Ser, Thr, Arg or Lys. Alternatively, X2 is Gly, Val, Leu, Ile, Ser, Thr or Met, and X8 is Asp, Glu, Asn, Glu (preferred), His, Arg or Lys (preferred). P2 is human albumin having the 585 amino acid sequence defined in the specification, an N-terminal fragment of albumin, or the Fc portion of a human immunoglobulin (Ig) selected from IgG1, IgG2, IgG3, IgG4, IgE, IgA, IgD, or IgM. The Fc portion (a 232 amino acid sequence defined in the specification) comprises the hinge, CH2, and CH3 domains. Preferred Host Cell: (IV) is a Chinese Hamster Ovary (CHO) cell.

ACTIVITY - Antidiabetic; Anorectic. No supporting biological data is given.

MECHANISM OF ACTION - None given. No supporting biological data is given.

USE - (I) is useful for normalizing blood glucose levels in mammal, for treating a patient with non-insulin diabetes mellitus or obesity, or for the manufacture of medicament for treating the above mentioned diseases (claimed).

ADMINISTRATION - (I) is **administered** by parenteral, oral, rectal, nasal, or lower respiratory route. No dosage details are given.

EXAMPLE - Construction of a DNA encoding a heterologous fusion protein such as V8-glucagon like peptide 1 (GLP-1) (7-37)-Fc was as follows: A Fc portion of human immunoglobulin (Ig)G1 was isolated from a cDNA library and contained the full hinge region and the CH2 and CH3 domains. A fragment containing 696 base pairs of this Fc portion of human IgG1 was subcloned into the NheI and Eco47III sites of mammalian expression vector pJBO2 to create pJBO2/Fc. DNA encoding the Igkappa secretion signal sequence fused to V8-GLP-1 (7-37) was generated by in vitro hybridization of four overlapping and complementary oligonucleotides such as 5'-CTAGCCACCATGGAGACAGACACACTCCTGCTATGGGTACTGCTG CTCTGGGTTCCAGGTTCCACTGGTGACCAGTG-3', 5'-GAGGGCACCTTCACCTCCGACGTGTCCTCCTAT CTGGAGGGCCAGGCCGCCAAGGAGTTCATCGCCTGGCTGGTGAAGGGAAGAGGC-3', 5'-TGAAGGTGCCCTCCACGTGGTCACCAGTGGAACCTGGAACCCAGAGCAGCAGTACCCATAGCAGGAGTGT GTCTGTCTCCATGGTGG-3', or 5'-GCCTCTTCCCTTCACCAGCCAGGCGATGAACTCCTTGGCGGCCTG GCCCTCCAGATAGGAGGACACGTCGGAGG-3'. The hybridization reaction was carried out using equivalent amounts of each oligonucleotide. The mixture of oligonucleotides was heated for 5 minutes at 100 degrees Centigrade in a ligation buffer and then cooled. The resulting hybridization product was ligated for 2 hours at room temperature or overnight at 16 degrees Centigrade to the pJBO2/Fc vector backbone which had been digested with NheI and Eco47III. The ligation products were used to transform competent XL-1 Blue cells. Recombinant plasmids were screened for the presence of peptide coding inserts by digesting clones with NcoI (encoding the Kozak sequence and first M of the signal peptide) and sequenced. The resulting expression plasmid used for transfection assays was denoted pJBO2-V8-GLP-1-Fc.(200 pages)

L149 ANSWER 34 OF 55 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2002:396077 CAPLUS
DOCUMENT NUMBER: 137:196575
TITLE: Exendin-4 as a stimulator of rat insulin I gene promoter activity via bZIP/CRE interactions sensitive to serine/threonine protein kinase inhibitor Ro 31-8220
AUTHOR(S): Chepurny, Oleg G.; Hussain, Mehboob A.; Holz, George G.
CORPORATE SOURCE: Departments of Physiology and Neuroscience, New York University School of Medicine, New York, NY, 10016, USA
SOURCE: Endocrinology (2002), 143(6), 2303-2313
CODEN: ENDOAO; ISSN: 0013-7227
PUBLISHER: Endocrine Society
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Signal transduction properties of exendin-4 (Ex-4) underlying its ability to stimulate rat insulin I gene promoter (RIP1) activity were assessed in the pancreatic β-cell line INS-1. Ex-4 acted via glucagon-like

peptide-1 receptors to stimulate RIP1 in a glucose-dependent manner, as measured in cells transfected with a -410-bp RIP1-luciferase construct (RIP1-Luc). The action of Ex-4 was independent of cAMP and PKA because it was not blocked by cotransfection with dominant-neg. Gαs, was unaffected by pretreatment with the membrane-permeant cAMP antagonist 8-Br-Rp-cAMPS, and remained apparent after treatment with PKA inhibitors H-89 or KT 5720. Similarly, cotransfection with a dominant-neg. isoform of the type-2 cAMP-regulated guanine nucleotide exchange factor (Epac2) failed to alter the response to Ex-4. Ro 31-8220, a serine/threonine protein kinase inhibitor that targets PKC as as well as the 90-kDa ribosomal S6 kinase (RSK) and mitogen- and stress-activated protein kinase (MSK) family of cAMP response element-binding protein (CREB) kinases, blocked the stimulatory action of Ex-4 at RIP1-Luc. However, selective inhibition of PKC using K-252c, prolonged exposure to phorbol 1,2-myristate-13-acetate, or cotransfection with dominant-neg. atypical PKC-ξ, was without effect. A-CREB, a dominant-neg. inhibitor of basic region-leucine zipper transcription factors (bZIPs) related in structure to CREB, inhibited the action of Ex-4 at RIP1-Luc, whereas A-ATF-2 was ineffective. Similarly, introduction of deletions at the RIP1 cAMP response element (CRE), or truncation of RIP1 to remove the CRE, nearly abolished the action of Ex-4. Inactivating mutations introduced at the A4/A3 elements, binding sites for the glucose-regulated homeodomain transcription factor PDX-1, did not diminish the response to Ex-4, although a marked reduction of basal promoter activity was observed The glucose-dependent stimulation of RIP1-Luc by Ex-4 was reproduced using a synthetic reporter (RIP1-CRE-Luc) incorporating multimerized CREs of the RIP1 nonpalindromic sequence 5'-TGACGTCC-3'. It is concluded that the bZIP and CRE-mediated stimulation of RIP1 by Ex-4 explains, at least in part, how this insulinotropic hormone facilitates transcriptional activity of the rat insulin I gene.

REFERENCE COUNT: 59 THERE ARE 59 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L149 ANSWER 35 OF 55 CAPLUS COPYRIGHT 2004 ACS on STN

ACCESSION NUMBER: 2002:231417 CAPLUS
DOCUMENT NUMBER: 137:88242
TITLE: The insulinotropic effect of acute exendin-4 administered to humans: comparison of nondiabetic state to type 2 diabetes
AUTHOR(S): Egan, Josephine M.; Clocquet, Astrid R.; Elahi, Dariush
CORPORATE SOURCE: Diabetes and Metabolism Section, Laboratory of Clinical Investigation, Gerontology Research Center, National Institute on Aging, National Institutes of Health, Baltimore, MD, 21224, USA
SOURCE: Journal of Clinical Endocrinology and Metabolism (2002), 87(3), 1282-1290
CODEN: JCEMAZ; ISSN: 0021-972X
PUBLISHER: Endocrine Society
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Exendin-4 is a potent and long-acting agonist of the glucagon-like peptide-1 (GLP-1) receptor. GLP-1 is an insulinotropic gut peptide and is being evaluated for the regulation of plasma glucose in type 2 diabetes. The purpose of the present study was to ascertain whether exendin-4 is insulinotropic and whether it has long-lived biol. effects in nondiabetic and type 2 diabetic subjects. Because incretins are glucose dependent with respect to their insulin-releasing capacity, we used the hyperglycemic glucose clamp technique to begin to address these issues in two sep. protocols. In one protocol, we infused exendin-4 (0.15 pmol·kg-1·min-1) in seven nondiabetic and seven type 2 diabetic subjects during the second hour of a 5-h hyperglycemic clamp in which fasting plasma glucose was raised by 5.4 mmol/L. The second protocol was identical to the first except that plasma glucose was allowed to fall to the fasting levels during the fourth hour and again raised by 5.4 mmol/L during the fifth hour in four nondiabetic and four diabetic

subjects. With the initiation of exendin-4 infusion at 60 min, plasma insulin response was potentiated 4- to 5-fold in both groups. Despite termination of exendin-4 at the end of the second hour, the insulin levels remained elevated for several hours and hyperglycemia was maintained. All volunteers ate a meal 5.5 h after inducing hyperglycemia. Postprandial plasma glucose, insulin, and GLP-1 did not rise in any subject, possibly because of delayed gastric emptying by exendin-4 even though its infusion had been terminated 4 h previously. We concluded that exendin-4 is a potent and long-lasting insulinotropic agent in nondiabetic and diabetic subjects.

REFERENCE COUNT: 11 THERE ARE 11 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L149 ANSWER 36 OF 55 USPATFULL on STN
ACCESSION NUMBER: 2001:226593 USPATFULL
TITLE: Long lasting insulinotropic peptides
INVENTOR(S): Bridon, Dominique P., Outremont, Canada
L'Archeveque, Benoit, Laval, Canada
Ezrin, Alan M., Moraga, CA, United States
Holmes, Darren L., Montreal, Canada
Leblanc, Anouk, Montreal, Canada
St. Pierre, Serge, Ile Bizard, Canada
PATENT ASSIGNEE(S): Conjuchem, Inc., Montreal, Canada (non-U.S. corporation)

	NUMBER	KIND	DATE	
PATENT INFORMATION:	US 6329336	B1	20011211	
	WO 2000069911		20001123	
APPLICATION INFO.:	US 2000-623618		20000905	(9)
	WO 2000-US13563		20000517	
			20000905	PCT 371 date
			20000905	PCT 102(e) date

	NUMBER	DATE
PRIORITY INFORMATION:	US 1999-134406P	19990517 (60)
	US 1999-159783P	19991015 (60)

DOCUMENT TYPE: Utility
FILE SEGMENT: GRANTED
PRIMARY EXAMINER: Horlick, Kenneth R.
ASSISTANT EXAMINER: Strzelecka, Teresa
LEGAL REPRESENTATIVE: Morrison & Foerster LLP
NUMBER OF CLAIMS: 14
EXEMPLARY CLAIM: 1
LINE COUNT: 2101
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB Modified insulinotropic peptides are disclosed. The modified insulinotropic peptides are capable of forming a peptidase stabilized insulinotropic peptide. The modified insulinotropic peptides are capable of forming covalent bonds with one or more blood components to form a conjugate. The conjugates may be formed in vivo or ex vivo. The modified peptides are administered to treat humans with diabetes and other related diseases.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L149 ANSWER 37 OF 55 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2002:283893 CAPLUS
DOCUMENT NUMBER: 137:150036
TITLE: Exendin-4, a GLP-1 receptor agonist, stimulates entero-insular axis in the rat, through a mechanism involving adrenal medulla
AUTHOR(S): Malendowicz, Ludwik K.; Nowak, Krzysztof W.; Zyterska, Agnieszka; Nussdorfer, Gastone G.; Macchi, Carlo; Nowak, Magdalena

CORPORATE SOURCE: Department of Histology and Embryology, School of Medicine, PL-60781, Pol.
SOURCE: Biomedical Research (2001), 22(6), 295-297
CODEN: BRESD5; ISSN: 0388-6107
PUBLISHER: Biomedical Research Press
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Glucagon-like peptide-1 (GLP-1) is known to lower blood glucose level, the effect depending on the stimulation of insulin and the inhibition of glucagon secretion. Due to the rapid inactivation of GLP-1 by dipeptidyl peptidase-IV (DPP-IV), its biol. action is very short. Hence, we investigated the effect on rat entero-insular axis of Exendin-4, a DPP-IV-resistant agonist of GPL-1 receptors. As expected the bolus administration of Exendin-4 (12 nmol/kg) increased the plasma concentration of insulin and decreased the blood levels of both glucagon and leptin in normal rats; however, GLP-1 raised glycemia. Exendin-4 did not evoke any effect in rats bearing enucleated-regenerated adrenals deprived of medullary tissue, thereby suggesting that its stimulating effect of entero-insular axis occurs via an indirect mechanism probably involving medullary catecholamines. Catecholamines are potent stimulator of hepatic glycogenolysis, and this may tentatively explain the hyperglycemizing effect of Exendin-4.

REFERENCE COUNT: 11 THERE ARE 11 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L149 ANSWER 38 OF 55 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2002:283888 CAPLUS
DOCUMENT NUMBER: 137:150035
TITLE: Exendin-4, a GLP-1 receptor agonist, stimulates rat pituitary-adrenocortical axis
AUTHOR(S): Malendowicz, Ludwik K.; Nowak, Krzysztof W.; Nussdorfer, Gastone G.; Zyterska, Agnieszka; Rebuffat, Piera; Nowak, Magdalena
CORPORATE SOURCE: Department of Histology and Embryology, Poznan School of Medicine, Poznan, PL-60781, Pol.
SOURCE: Biomedical Research (2001), 22(6), 273-276
CODEN: BRESD5; ISSN: 0388-6107
PUBLISHER: Biomedical Research Press
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Preproglucagon-derived peptides, among which glucagon and glucagon-like peptide-1 (GLP-1), are known to modulate the activity of the hypothalamo-pituitary-adrenal (HPA) axis. Many effects of GPL-1, however, are prevented by its very short half-life. Hence we investigated in vivo and in vitro the effects on the rat HPA axis of the GLP-1-receptor agonist exendin-4 (EX4), which possesses a longer biol. half-life than GLP-1. The bolus systemic administration of EX4 (12 nmol/kg) evoked significant rises in ACTH, aldosterone and corticosterone concns. EX4 (10-7 M) induced a weak but significant increase in corticosterone secretion from dispersed rat adrenocortical cells, and the effect was abrogated by the GLP-1-receptor antagonist exendin (9-39). Collectively, our findings indicate that EX4, acting via GLP-1 receptors, stimulates HPA axis in rats, acting on both its central (hypothalamo-pituitary) and peripheral (adrenocortical) branch.

REFERENCE COUNT: 16 THERE ARE 16 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L149 ANSWER 39 OF 55 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2001:660036 CAPLUS
DOCUMENT NUMBER: 136:335063
TITLE: Synergistic insulinotropic effects of succinic acid dimethyl ester and exendin-4 in anaesthetized rats
AUTHOR(S): Cancelas, Jesus; Villanueva-Penacarrillo, Maria L.; Valverde, Isabel; Malaisse, Willy J.
CORPORATE SOURCE: Fundacion Jimenez Diaz, Madrid, 28040, Spain
SOURCE: International Journal of Molecular Medicine (2001),

8(3), 269-271
CODEN: IJMMFG; ISSN: 1107-3756
PUBLISHER: International Journal of Molecular Medicine
DOCUMENT TYPE: Journal
LANGUAGE: English

AB It was recently proposed that suitable succinic acid esters could be used to potentiate the insulinotropic action of glucagon-like peptide 1 (GLP-1) in the treatment of type-2 diabetes mellitus. In such a perspective, the present study aimed mainly at investigating whether exendin-4 (Ex-4), a peptide structurally related to GLP-1(7-36)amide, and succinic acid di-Me ester (SAD) also act synergistically upon insulin secretion in anesthetized rats. Despite a higher plasma insulin concentration in SAD-infused rats (5.5±1.1 ng/mL) than in saline-infused animals (1.9±0.7 ng/mL), the i.v. injection of Ex-4 augmented to a greater extent the plasma concentration of insulin in the former rats (+7.4±2.5 ng/mL) than in the latter animals (+2.8±0.6 ng/mL). These findings document that the insulinotropic actions of Ex-4 and GLP-1 display comparable nutrient dependency, being both potentiated by a non-glycidic nutrient secretagogue such as SAD.

REFERENCE COUNT: 10 THERE ARE 10 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L149 ANSWER 40 OF 55 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2001:812439 CAPLUS
DOCUMENT NUMBER: 136:128554
TITLE: Pharmacokinetic actions of exendin-4 in the rat: comparison with glucagon-like peptide-1
AUTHOR(S): Parkes, David; Jodka, Carolyn; Smith, Pam; Nayak, Sonali; Rinehart, Liz; Gingerich, Ron; Chen, Kim; Young, Andrew
CORPORATE SOURCE: Amylin Pharmaceuticals Inc., San Diego, CA, 92121, USA
SOURCE: Drug Development Research (2001), 53(4), 260-267
CODEN: DDREDK; ISSN: 0272-4391
PUBLISHER: Wiley-Liss, Inc.
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Exendin-4, originally isolated from saliva of the lizard Heloderma suspectum, shares 53% sequence homol. and several potentially antidiabetic actions with the mammalian hormone glucagon-like peptide-1 (7-36)amide (GLP-1). It shows a higher potency and longer duration of effect in vivo, which may be partly attributed to pharmacokinetic properties. The present study compares the pharmacokinetics of GLP-1 and exendin-4 in rats after i.v. (iv), s.c. (s.c.), or i.p. (i.p.) administration. Samples were assayed for active GLP-1 (7-36) amide using an ELISA that does not detect GLP-1 (1-36-amide), (1-37), (9-36-amide) or (9-37). In parallel expts., samples were assayed for exendin-4 using a two-site immunoradiometric assay that reacts specifically with full-length exendin-4. The estimated half-life for GLP-1 and exendin-4 were 0.8-4.7 min and 18-41 min for iv bolus, and 4.6-7.1 min and 90-216 min for SC administration, resp. Half-lives after i.p. injection were 0.6-13.5 min for GLP-1 and 125-174 min for exendin-4. Bioavailability for GLP-1 and exendin-4 was 44-71% and 65-75%, resp., for s.c. injection. For i.p. injection, bioavailability for GLP-1 and exendin-4 was 36-67% and 74-76%, resp. Plasma clearance, as determined from iv infusion data, was 35-38 mL/min for GLP-1 and 4-8 mL/min for exendin-4. Both Co/Cmax and AUC values were proportional to dose with each route of administration. Plasma clearance of exendin-4 was reduced by 4.4-fold in nephrectomized animals. In conclusion, exendin-4 exhibited a much longer plasma half-life than GLP-1 in rats after iv, s.c., or i.p. injection, which may contribute in some part to reported differences in duration of biol. action of the 2 peptides.

REFERENCE COUNT: 26 THERE ARE 26 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L149 ANSWER 41 OF 55 SCISEARCH COPYRIGHT 2004 THOMSON ISI on STN
ACCESSION NUMBER: 2000:899752 SCISEARCH
THE GENUINE ARTICLE: 364KW

TITLE: Scintigraphic detection of insulinomas by [I-123]glucagon-like peptide-1 and its analogue [I-123]-**exendin4** [Y39] in a rat tumor model.
AUTHOR: Gotthardt M (Reprint); Fischer M; Baltes N; Brandt D; Welcke U; Goeke B J; Joseph K
CORPORATE SOURCE: UNIV MARBURG, SCH MED, MARBURG, GERMANY; INSEL SPITAL, BERN, SWITZERLAND
COUNTRY OF AUTHOR: GERMANY; SWITZERLAND
SOURCE: JOURNAL OF NUCLEAR MEDICINE, (MAY 2000) Vol. 41, No. 5, Supp. [S], pp. 31-31.
Publisher: SOC NUCLEAR MEDICINE INC, 1850 SAMUEL MORSE DR, RESTON, VA 20190-5316.
ISSN: 0161-5505.
DOCUMENT TYPE: Conference; Journal
FILE SEGMENT: LIFE; CLIN
LANGUAGE: English
REFERENCE COUNT: 0

L149 ANSWER 42 OF 55 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2000:200908 CAPLUS
DOCUMENT NUMBER: 133:69247
TITLE: The hepatic vagal reception of intraportal GLP-1 is via receptor different from the pancreatic GLP-1 receptor
AUTHOR(S): Nishizawa, M.; Nakabayashi, H.; Kawai, K.; Ito, T.; Kawakami, S.; Nakagawa, A.; Niijima, A.; Uchida, K.
CORPORATE SOURCE: Division of Endocrinology, Dep. of Intern. Med., Kanazawa Med. University, Uchinada, Japan
SOURCE: Journal of the Autonomic Nervous System (2000), 80(1,2), 14-21
CODEN: JASYDS; ISSN: 0165-1838
PUBLISHER: Elsevier Science B.V.
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Glucagon-like peptide-1 (7-36)amide (tGLP-1), a representative humoral incretin, released into the portal circulation in response to a meal ingestion, exerts insulinotropic action through binding to the tGLP-1 receptor known to be a single mol. form thus far. The authors previously reported that the hepatic vagal nerve is receptive to intraportal tGLP-1, but not to non-insulinotropic full-length GLP-1-(1-37), through a mechanism mediated by specific receptor to the hormone. In the present study, the authors aimed to examine how modification of the receptor function alters this neural reception of tGLP-1, by the specific agonist, exendin-4, and the specific antagonist, exendin (9-39)amide, of the receptor at doses known to exert their effects on the insulinotropic action of tGLP-1. Intraportal injection of 0.2 or 4.0 pmol tGLP-1, a periphysiol. and pharmacol. dose, resp., facilitated the afferent impulse discharge rate of the hepatic vagus in anesthetized rats, as reported previously. However, unexpectedly, intraportal injection of exendin-4 at a dose of 0.2 or 4.0 pmol, or of even 40.0 pmol, did not facilitate the afferents at all. Moreover, intraportal injection of exendin (9-39)amide at 100 times or more molar dose to that of tGLP-1, either 5 min before or 10 min after injection of 0.2 or 4.0 pmol tGLP-1, failed to modify the tGLP-1-induced facilitation of the afferents. The present results suggest that the neural reception of tGLP-1 involves a receptor mechanism distinct from that in the well-known humoral insulinotropic action.
REFERENCE COUNT: 51 THERE ARE 51 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L149 ANSWER 43 OF 55 BIOSIS COPYRIGHT 2004 BIOLOGICAL ABSTRACTS INC. on STN
ACCESSION NUMBER: 2000:294886 BIOSIS
DOCUMENT NUMBER: PREV200000294886
TITLE: Scintigraphic detection of insulinomas by (123I)-Glucagon-Like Peptide-1 and its analogue (123I)-**Exendin4**(Y39) in a rat tumor model.
AUTHOR(S): Gotthardt, M. [Reprint author]; Fischer, M.; Baltes, N.;

Brandt, D.; Welcke, U.; Goeke, B. J.; Joseph, K.
CORPORATE SOURCE: Philipps-University School of Medicine, Marburg, Germany
SOURCE: Journal of Nuclear Medicine, (May, 2000) Vol. 41, No. 5 Suppl., pp. 9P. print.
Meeting Info.: 47th Annual Meeting of the Society of Nuclear Medicine. St. Louis, Missouri, USA. June 03-07, 2000. Society of Nuclear Medicine.
CODEN: JNMEAQ. ISSN: 0161-5505.
DOCUMENT TYPE: Conference; (Meeting)
Conference; Abstract; (Meeting Abstract)
LANGUAGE: English
ENTRY DATE: Entered STN: 6 Jul 2000
Last Updated on STN: 7 Jan 2002

L149 ANSWER 44 OF 55 SCISEARCH COPYRIGHT 2004 THOMSON ISI on STN
ACCESSION NUMBER: 1999:379716 SCISEARCH
THE GENUINE ARTICLE: 194VL
TITLE: Glucose-lowering and insulin-sensitizing actions of exendin-4 - Studies in obese diabetic (ob/ob, db/db) mice, diabetic fatty Zucker rats, and diabetic rhesus monkeys (Macaca mulatta)
AUTHOR: Young A A (Reprint); Gedulin B R; Bhavsar S; Bodkin N; Jodka C; Hansen B; Denaro M
CORPORATE SOURCE: AMYLIN PHARMACEUT, 9373 TOWNE CTR DR, SAN DIEGO, CA 92121 (Reprint); UNIV MARYLAND, OBES & DIABET RES CTR, BALTIMORE, MD 21201
COUNTRY OF AUTHOR: USA
SOURCE: DIABETES, (MAY 1999) Vol. 48, No. 5, pp. 1026-1034.
Publisher: AMER DIABETES ASSOC, 1660 DUKE ST, ALEXANDRIA, VA 22314.
ISSN: 0012-1797.
DOCUMENT TYPE: Article; Journal
FILE SEGMENT: LIFE; CLIN
LANGUAGE: English
REFERENCE COUNT: 50
ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB Exendin-4 is a 39 amino acid peptide isolated from the salivary secretions of the Gila monster (Heloderma suspectum). It shows 53% sequence similarity to glucagon-like peptide (GLP)-1. Unlike GLP-1, **exendin4** has a prolonged glucose-lowering action in vivo. We compared the potency and duration of glucose-lowering effects of exendin-4 and GLP-1 in hyperglycemic db/db and ob/ob mice. Whereas reductions in plasma glucose of up to 35% vanished within 1 h with most doses of GLP-1, the same doses of exendin-4 resulted in a similar glucose-lowering effect that persisted for >4 h. Exendin-4 was 5,530-fold more potent than GLP-1 in db/db mice (effective doses, 50% [ED(50)s] of 0.059 mu g/kg +/- 0.15 log and 329 mu g/kg +/- 0.22 log, respectively) and was 5,480-fold more potent in ob/ob mice (ED(50)s of 0.136 mu g/kg +/- 0.10 log and 744 mu g/kg +/- 0.21 log, respectively) when the percentage fall in plasma glucose at 1 h was used as the indicator response. Exendin-4 dose-dependently accelerated glucose lowering in diabetic rhesus monkeys by up to 37% with an ED50 of 0.25 mu g/kg +/- 0.09 log. In two experiments in which diabetic fatty Zucker rats were injected subcutaneously twice daily for 5-6 weeks with doses of exendin-4 up to 100 mu g . rat(-1) . day(-1) (similar to 250 mu g/kg), HbA(1c) was reduced relative to saline-injected control rats. Exendin-4 treatment was also associated in each of these experiments with weight loss and improved insulin sensitivity, as demonstrated by increases of up to 32 and 49%, respectively, in the glucose infusion rate (GIR) in the hyperinsulinemic euglycemic clamp. ED(50)s for weight loss and the increase in clamp GIR were 1.0 mu g/kg +/- 0.15 log and 2.4 mu g/kg +/- 0.41 log, respectively. In conclusion, acute and chronic administration of exendin-4 has demonstrated an antidiabetic effect in several animal models of type 2 diabetes.

L149 ANSWER 45 OF 55 CAPLUS COPYRIGHT 2004 ACS on STN

ACCESSION NUMBER: 1998:287874 CAPLUS
DOCUMENT NUMBER: 129:78077
TITLE: Molecular cloning of the helodermin and exendin-4 cDNAs in the lizard. Relationship to vasoactive intestinal polypeptide/pituitary adenylate cyclase activating polypeptide and glucagon-like peptide 1 and evidence against the existence of mammalian homologues
AUTHOR(S): Pohl, Markus; Wank, Stephen A.
CORPORATE SOURCE: Digestive Diseases Branch, NIDDK, Natl. Inst. of Health, Bethesda, MD, 20892, USA
SOURCE: Journal of Biological Chemistry (1998), 273(16), 9778-9784
CODEN: JBCHA3; ISSN: 0021-9258
PUBLISHER: American Society for Biochemistry and Molecular Biology
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Helodermin and exendin-4, two peptides isolated from the salivary gland of the Gila monster, Heloderma suspectum, are approx. 50% homologous to vasoactive intestinal peptide (VIP) and glucagon-like peptide-1 (GLP-1), resp., and interact with the mammalian receptors for VIP and GLP-1 with equal or higher affinity and efficacy. Immunohistochem. studies suggested the presence of helodermin-like peptides in mammals. To determine whether helodermin and exendin-4 are present in mammals and their evolutionary relationship to VIP and GLP-1, their cDNAs were first cloned from Gila monster salivary gland. Northern blots and reverse transcription-polymerase chain reaction of multiple Gila monster tissues identified .apprx.500-base pair transcripts only from salivary gland. Both helodermin and exendin-4 full-length cDNAs were .apprx.500 base pairs long, and they encoded precursor proteins containing the entire amino acid sequence of helodermin and exendin-4, as well as a 44- or 45-amino acid N-terminal extension peptide, resp., having .apprx.60% homol. The size and structural organization of these cDNAs indicated that they are closely related to one another but markedly different from known cDNAs for the VIP/GLP-1 peptide family previously identified in both lower and higher evolved species. Cloning of the Gila monster VIP/peptide histidine isoleucine, pituitary adenylate cyclase activating polypeptide, and glucagon/GLP-1 cDNAs and Southern blotting of Gila monster DNA demonstrate the coexistence of sep. genes for these peptides and suggests, along with the restricted salivary gland expression, that helodermin and exendin-4 coevolved to serve a sep. specialized function. Probing of a variety of rat and human tissues on Northern blots, human and rat Southern blots, and genomic and cDNA libraries with either helodermin- or exendin-4-specific cDNAs failed to identify evidence for mammalian homologs. These data indicate that helodermin and exendin-4 are not the precursors to VIP and GLP-1 and that they belong to a sep. peptide family encoded by sep. genes. Furthermore, the existence of as yet undiscovered mammalian homologs to helodermin and exendin-4 seems unlikely.

REFERENCE COUNT: 45 THERE ARE 45 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L149 ANSWER 46 OF 55 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 1997:286809 CAPLUS
DOCUMENT NUMBER: 127:13296
TITLE: Exendin-4 agonist and exendin(9-39)amide antagonist of the GLP-1(7-36)amide effects in liver and muscle
AUTHOR(S): Alcantara, Ana I.; Morales, Monica; Delgado, Elena; Lopez-Delgado, Maria I.; Clemente, Felipe; Luque, Miguel A.; Malaisse, Willy J.; Valverde, Isabel; Villanueva-Penacarrillo, Maria L.
CORPORATE SOURCE: Dep. Metab., Nutricion Hormonas, Fundacion Jimenez Diaz, Madrid, 28040, Spain
SOURCE: Archives of Biochemistry and Biophysics (1997), 341(1), 1-7
CODEN: ABBIA4; ISSN: 0003-9861
PUBLISHER: Academic

DOCUMENT TYPE: Journal
LANGUAGE: English
AB The GLP-1 structurally related peptides exendin-4 and exendin(9-39)amide were found to act, in rat liver and skeletal muscle, as agonist and antagonist, resp., of the GLP-1(7-36)amide effects on glucose metabolism Thus, like GLP-1(7-36)amide, exendin-4 increased glycogen synthase a activity and glucose incorporation into glycogen in both tissues and also stimulated exogenous D-glucose utilization and oxidation in muscle. These effects of GLP-1(7-36)amide and exendin-4 were inhibited by exendin(9-39)amide. Our findings provide further support to the proposed use of GLP-1, or exendin-4, as a tool in the treatment of diabetes mellitus. Thus, in addition to the well-known insulinotropic action of the peptides, they act both in liver and in muscle in a manner most suitable for restoration of glucose homeostasis, with emphasis on their pos. effects upon glycogen synthesis in the two tissues and on the stimulation of exogenous glucose catabolism in muscle.

L149 ANSWER 47 OF 55 IFIPAT COPYRIGHT 2004 IFI on STN DUPLICATE 14
AN 02614550 IFIPAT;IFIUDB;IFICDB
TITLE: EXENDIN-3 AND **EXENDIN-4** POLYPEPTIDES, AND **PHARMACEUTICAL COMPOSITIONS** COMPRISING SAME; TREATMENT OF DIABETES MELLITUS AND PREVENTION OF HYPERGLYCEMIA
INVENTOR(S): Eng, John, 5427 Arlington Ave, Bronx, NY, 10471
PATENT ASSIGNEE(S): Unassigned
PRIMARY EXAMINER: Draper, Garnette D
ASSISTANT EXAMINER: Kemmerer, Elizabeth C
AGENT: Allegretti & Witcoff, Ltd

	NUMBER	PK	DATE
PATENT INFORMATION:	US 5424286	A	19950613
	(CITED IN 007 LATER PATENTS)		
APPLICATION INFORMATION:	US 1993-66480		19930524
EXPIRATION DATE:	24 May 2013		
FAMILY INFORMATION:	US 5424286		19950613
DOCUMENT TYPE:	Utility		
FILE SEGMENT:	CHEMICAL		
	GRANTED		
OTHER SOURCE:	CA 123:74913		

GOVERNMENT INTEREST:
This U.S. Government has a paid-up license in this invention and the right in limited circumstances to require the patent owner to license others on reasonable terms as provided for by the terms of the agreement with the Department of Veterans Affairs, reference number 024I, GPB No. 20-560.

NUMBER OF CLAIMS: 7
GRAPHICS INFORMATION: 9 Drawing Sheet(s), 9 Figure(s).
AB This invention encompasses **pharmaceutical compositions** containing exendin-3 or **exendin-4**, fragments thereof, or any combination thereof, and methods for the treatment of diabetes mellitus and the prevention of hyperglycemia.
CLMN 7
GI 9 Drawing Sheet(s), 9 Figure(s).

L149 ANSWER 48 OF 55 DGENE COPYRIGHT 2004 THOMSON DERWENT on STN
ACCESSION NUMBER: ADH22053 DNA DGENE
TITLE: New albumin fusion protein, useful for preparing a composition for treating diabetes mellitus.
INVENTOR: Rosen C A; Haseltine W A
PATENT ASSIGNEE: (HUMA-N)HUMAN GENOME SCI INC.
PATENT INFO: WO 2003059934 A2 20030724 999p
APPLICATION INFO: WO 2002-US40892 20021223
PRIORITY INFO: US 2001-341811P 20011221
US 2002-350358P 20020124

US 2002-359370P 20020226
US 2002-360000P 20020228
US 2002-367500P 20020327
US 2002-370227P 20020408
US 2002-378950P 20020510
US 2002-398008P 20020724
US 2002-402131P 20020809
US 2002-402708P 20020813
US 2002-411355P 20020918
US 2002-414984P 20021002
US 2002-417611P 20021011
US 2002-420246P 20021023
US 2002-423623P 20021105

DOCUMENT TYPE: Patent
LANGUAGE: English
OTHER SOURCE: 2003-598501 [56]
DESCRIPTION: **Exendin4** codon optimised oligo EXTC-1, SEQ ID NO:850.

AN ADH22053 DNA DGENE

AB The invention relates to fusion proteins comprising human serum albumin (ADH21530) and a therapeutic polypeptide such as a therapeutic protein, antibody or peptide or their variants or fragments. The therapeutic protein may be fused to the N-terminus, the C-terminus or both termini of albumin via a linker. The albumin component of the fusion proteins prolongs the shelf-life and the in vitro and vivo biological activity of the proteins compared with those of the corresponding therapeutic proteins on their own. The invention also relates to nucleic acids encoding albumin fusion proteins, vectors and host cells comprising an albumin fusion protein nucleic acid, compositions and kits comprising an albumin fusion protein, the method of extending the shelf-life of a therapeutic protein by fusion with albumin, and the treatment of disease using an albumin fusion protein. The albumin fusion proteins may be used in the treatment of metabolic/endocrine disorders, diabetes and diabetes-related conditions. Specifically the albumin fusion proteins may be used to treat type 1 and type 2 diabetes, hyperglycaemia, neural disorders (especially neuropathy), retinopathy, cardiovascular disorders (especially heart disease, renal disorders and obesity. The proteins may also be used in a method of maintaining a basal glucose level in a patient and in a method for losing weight. The present sequence is related to the invention.

L149 ANSWER 49 OF 55 DGENE COPYRIGHT 2004 THOMSON DERWENT on STN
ACCESSION NUMBER: ADH22058 DNA DGENE
TITLE: New albumin fusion protein, useful for preparing a composition for treating diabetes mellitus.
INVENTOR: Rosen C A; Haseltine W A
PATENT ASSIGNEE: (HUMA-N)HUMAN GENOME SCI INC.
PATENT INFO: WO 2003059934 A2 20030724 999p
APPLICATION INFO: WO 2002-US40892 20021223
PRIORITY INFO: US 2001-341811P 20011221
US 2002-350358P 20020124
US 2002-359370P 20020226
US 2002-360000P 20020228
US 2002-367500P 20020327
US 2002-370227P 20020408
US 2002-378950P 20020510
US 2002-398008P 20020724
US 2002-402131P 20020809
US 2002-402708P 20020813
US 2002-411355P 20020918
US 2002-414984P 20021002
US 2002-417611P 20021011
US 2002-420246P 20021023
US 2002-423623P 20021105

DOCUMENT TYPE: Patent
LANGUAGE: English

OTHER SOURCE: 2003-598501 [56]
DESCRIPTION: **Exendin4** codon optimised oligo EXTN-2, SEQ ID NO:855.

AN ADH22058 DNA DGENE

AB The invention relates to fusion proteins comprising human serum albumin (ADH21530) and a therapeutic polypeptide such as a therapeutic protein, antibody or peptide or their variants or fragments. The therapeutic protein may be fused to the N-terminus, the C-terminus or both termini of albumin via a linker. The albumin component of the fusion proteins prolongs the shelf-life and the in vitro and vivo biological activity of the proteins compared with those of the corresponding therapeutic proteins on their own. The invention also relates to nucleic acids encoding albumin fusion proteins, vectors and host cells comprising an albumin fusion protein nucleic acid, compositions and kits comprising an albumin fusion protein, the method of extending the shelf-life of a therapeutic protein by fusion with albumin, and the treatment of disease using an albumin fusion protein. The albumin fusion proteins may be used in the treatment of metabolic/endocrine disorders, diabetes and diabetes-related conditions. Specifically the albumin fusion proteins may be used to treat type 1 and type 2 diabetes, hyperglycaemia, neural disorders (especially neuropathy), retinopathy, cardiovascular disorders (especially heart disease, renal disorders and obesity. The proteins may also be used in a method of maintaining a basal glucose level in a patient and in a method for losing weight. The present sequence is related to the invention.

L149 ANSWER 50 OF 55 DGENE COPYRIGHT 2004 THOMSON DERWENT on STN
ACCESSION NUMBER: ADH22057 DNA DGENE
TITLE: New albumin fusion protein, useful for preparing a composition for treating diabetes mellitus.
INVENTOR: Rosen C A; Haseltine W A
PATENT ASSIGNEE: (HUMA-N) HUMAN GENOME SCI INC.
PATENT INFO: WO 2003059934 A2 20030724 999p
APPLICATION INFO: WO 2002-US40892 20021223
PRIORITY INFO: US 2001-341811P 20011221
US 2002-350358P 20020124
US 2002-359370P 20020226
US 2002-360000P 20020228
US 2002-367500P 20020327
US 2002-370227P 20020408
US 2002-378950P 20020510
US 2002-398008P 20020724
US 2002-402131P 20020809
US 2002-402708P 20020813
US 2002-411355P 20020918
US 2002-414984P 20021002
US 2002-417611P 20021011
US 2002-420246P 20021023
US 2002-423623P 20021105
DOCUMENT TYPE: Patent
LANGUAGE: English
OTHER SOURCE: 2003-598501 [56]
DESCRIPTION: **Exendin4** codon optimised oligo EXTN-1, SEQ ID NO:854.

AN ADH22057 DNA DGENE

AB The invention relates to fusion proteins comprising human serum albumin (ADH21530) and a therapeutic polypeptide such as a therapeutic protein, antibody or peptide or their variants or fragments. The therapeutic protein may be fused to the N-terminus, the C-terminus or both termini of albumin via a linker. The albumin component of the fusion proteins prolongs the shelf-life and the in vitro and vivo biological activity of the proteins compared with those of the corresponding therapeutic proteins on their own. The invention also relates to nucleic acids encoding albumin fusion proteins, vectors and host cells comprising an albumin fusion protein nucleic acid, compositions and kits comprising an albumin fusion protein, the method of extending the shelf-life of a

therapeutic protein by fusion with albumin, and the treatment of disease using an albumin fusion protein. The albumin fusion proteins may be used in the treatment of metabolic/endocrine disorders, diabetes and diabetes-related conditions. Specifically the albumin fusion proteins may be used to treat type 1 and type 2 diabetes, hyperglycaemia, neural disorders (especially neuropathy), retinopathy, cardiovascular disorders (especially heart disease, renal disorders and obesity. The proteins may also be used in a method of maintaining a basal glucose level in a patient and in a method for losing weight. The present sequence is related to the invention.

L149 ANSWER 51 OF 55 DGENE COPYRIGHT 2004 THOMSON DERWENT on STN
ACCESSION NUMBER: ADH22054 DNA DGENE
TITLE: New albumin fusion protein, useful for preparing a composition for treating diabetes mellitus.
INVENTOR: Rosen C A; Haseltine W A
PATENT ASSIGNEE: (HUMA-N)HUMAN GENOME SCI INC.
PATENT INFO: WO 2003059934 A2 20030724 999p
APPLICATION INFO: WO 2002-US40892 20021223
PRIORITY INFO: US 2001-341811P 20011221
US 2002-350358P 20020124
US 2002-359370P 20020226
US 2002-360000P 20020228
US 2002-367500P 20020327
US 2002-370227P 20020408
US 2002-378950P 20020510
US 2002-398008P 20020724
US 2002-402131P 20020809
US 2002-402708P 20020813
US 2002-411355P 20020918
US 2002-414984P 20021002
US 2002-417611P 20021011
US 2002-420246P 20021023
US 2002-423623P 20021105
DOCUMENT TYPE: Patent
LANGUAGE: English
OTHER SOURCE: 2003-598501 [56]
DESCRIPTION: **Exendin4** codon optimised oligo EXTC-2, SEQ ID NO:851.
AN ADH22054 DNA DGENE
AB The invention relates to fusion proteins comprising human serum albumin (ADH21530) and a therapeutic polypeptide such as a therapeutic protein, antibody or peptide or their variants or fragments. The therapeutic protein may be fused to the N-terminus, the C-terminus or both termini of albumin via a linker. The albumin component of the fusion proteins prolongs the shelf-life and the in vitro and vivo biological activity of the proteins compared with those of the corresponding therapeutic proteins on their own. The invention also relates to nucleic acids encoding albumin fusion proteins, vectors and host cells comprising an albumin fusion protein nucleic acid, compositions and kits comprising an albumin fusion protein, the method of extending the shelf-life of a therapeutic protein by fusion with albumin, and the treatment of disease using an albumin fusion protein. The albumin fusion proteins may be used in the treatment of metabolic/endocrine disorders, diabetes and diabetes-related conditions. Specifically the albumin fusion proteins may be used to treat type 1 and type 2 diabetes, hyperglycaemia, neural disorders (especially neuropathy), retinopathy, cardiovascular disorders (especially heart disease, renal disorders and obesity. The proteins may also be used in a method of maintaining a basal glucose level in a patient and in a method for losing weight. The present sequence is related to the invention.

L149 ANSWER 52 OF 55 DGENE COPYRIGHT 2004 THOMSON DERWENT on STN
ACCESSION NUMBER: ADH22060 DNA DGENE
TITLE: New albumin fusion protein, useful for preparing a composition for treating diabetes mellitus.

INVENTOR: Rosen C A; Haseltine W A
PATENT ASSIGNEE: (HUMA-N)HUMAN GENOME SCI INC.
PATENT INFO: WO 2003059934 A2 20030724 999p
APPLICATION INFO: WO 2002-US40892 20021223
PRIORITY INFO: US 2001-341811P 20011221
US 2002-350358P 20020124
US 2002-359370P 20020226
US 2002-360000P 20020228
US 2002-367500P 20020327
US 2002-370227P 20020408
US 2002-378950P 20020510
US 2002-398008P 20020724
US 2002-402131P 20020809
US 2002-402708P 20020813
US 2002-411355P 20020918
US 2002-414984P 20021002
US 2002-417611P 20021011
US 2002-420246P 20021023
US 2002-423623P 20021105
DOCUMENT TYPE: Patent
LANGUAGE: English
OTHER SOURCE: 2003-598501 [56]
DESCRIPTION: **Exendin4** codon optimised oligo EXTN-4, SEQ ID NO:857.

AN ADH22060 DNA DGENE
AB The invention relates to fusion proteins comprising human serum albumin (ADH21530) and a therapeutic polypeptide such as a therapeutic protein, antibody or peptide or their variants or fragments. The therapeutic protein may be fused to the N-terminus, the C-terminus or both termini of albumin via a linker. The albumin component of the fusion proteins prolongs the shelf-life and the in vitro and vivo biological activity of the proteins compared with those of the corresponding therapeutic proteins on their own. The invention also relates to nucleic acids encoding albumin fusion proteins, vectors and host cells comprising an albumin fusion protein nucleic acid, compositions and kits comprising an albumin fusion protein, the method of extending the shelf-life of a therapeutic protein by fusion with albumin, and the treatment of disease using an albumin fusion protein. The albumin fusion proteins may be used in the treatment of metabolic/endocrine disorders, diabetes and diabetes-related conditions. Specifically the albumin fusion proteins may be used to treat type 1 and type 2 diabetes, hyperglycaemia, neural disorders (especially neuropathy), retinopathy, cardiovascular disorders (especially heart disease, renal disorders and obesity. The proteins may also be used in a method of maintaining a basal glucose level in a patient and in a method for losing weight. The present sequence is related to the invention.

L149 ANSWER 53 OF 55 DGENE COPYRIGHT 2004 THOMSON DERWENT on STN
ACCESSION NUMBER: ADH22059 DNA DGENE
TITLE: New albumin fusion protein, useful for preparing a composition for treating diabetes mellitus.
INVENTOR: Rosen C A; Haseltine W A
PATENT ASSIGNEE: (HUMA-N)HUMAN GENOME SCI INC.
PATENT INFO: WO 2003059934 A2 20030724 999p
APPLICATION INFO: WO 2002-US40892 20021223
PRIORITY INFO: US 2001-341811P 20011221
US 2002-350358P 20020124
US 2002-359370P 20020226
US 2002-360000P 20020228
US 2002-367500P 20020327
US 2002-370227P 20020408
US 2002-378950P 20020510
US 2002-398008P 20020724
US 2002-402131P 20020809
US 2002-402708P 20020813
US 2002-411355P 20020918

US 2002-414984P 20021002
US 2002-417611P 20021011
US 2002-420246P 20021023
US 2002-423623P 20021105
DOCUMENT TYPE: Patent
LANGUAGE: English
OTHER SOURCE: 2003-598501 [56]
DESCRIPTION: **Exendin4** codon optimised oligo EXTN-3, SEQ ID NO:856.

AN ADH22059 DNA DGENE
AB The invention relates to fusion proteins comprising human serum albumin (ADH21530) and a therapeutic polypeptide such as a therapeutic protein, antibody or peptide or their variants or fragments. The therapeutic protein may be fused to the N-terminus, the C-terminus or both termini of albumin via a linker. The albumin component of the fusion proteins prolongs the shelf-life and the in vitro and vivo biological activity of the proteins compared with those of the corresponding therapeutic proteins on their own. The invention also relates to nucleic acids encoding albumin fusion proteins, vectors and host cells comprising an albumin fusion protein nucleic acid, compositions and kits comprising an albumin fusion protein, the method of extending the shelf-life of a therapeutic protein by fusion with albumin, and the treatment of disease using an albumin fusion protein. The albumin fusion proteins may be used in the treatment of metabolic/endocrine disorders, diabetes and diabetes-related conditions. Specifically the albumin fusion proteins may be used to treat type 1 and type 2 diabetes, hyperglycaemia, neural disorders (especially neuropathy), retinopathy, cardiovascular disorders (especially heart disease, renal disorders and obesity. The proteins may also be used in a method of maintaining a basal glucose level in a patient and in a method for losing weight. The present sequence is related to the invention.

L149 ANSWER 54 OF 55 DGENE COPYRIGHT 2004 THOMSON DERWENT on STN
ACCESSION NUMBER: ADH22056 DNA DGENE
TITLE: New albumin fusion protein, useful for preparing a composition for treating diabetes mellitus.
INVENTOR: Rosen C A; Haseltine W A
PATENT ASSIGNEE: (HUMA-N)HUMAN GENOME SCI INC.
PATENT INFO: WO 2003059934 A2 20030724 999p
APPLICATION INFO: WO 2002-US40892 20021223
PRIORITY INFO: US 2001-341811P 20011221
US 2002-350358P 20020124
US 2002-359370P 20020226
US 2002-360000P 20020228
US 2002-367500P 20020327
US 2002-370227P 20020408
US 2002-378950P 20020510
US 2002-398008P 20020724
US 2002-402131P 20020809
US 2002-402708P 20020813
US 2002-411355P 20020918
US 2002-414984P 20021002
US 2002-417611P 20021011
US 2002-420246P 20021023
US 2002-423623P 20021105
DOCUMENT TYPE: Patent
LANGUAGE: English
OTHER SOURCE: 2003-598501 [56]
DESCRIPTION: **Exendin4** codon optimised oligo EXTC-4, SEQ ID NO:853.

AN ADH22056 DNA DGENE
AB The invention relates to fusion proteins comprising human serum albumin (ADH21530) and a therapeutic polypeptide such as a therapeutic protein, antibody or peptide or their variants or fragments. The therapeutic protein may be fused to the N-terminus, the C-terminus or both termini of albumin via a linker. The albumin component of the fusion proteins

prolongs the shelf-life and the in vitro and vivo biological activity of the proteins compared with those of the corresponding therapeutic proteins on their own. The invention also relates to nucleic acids encoding albumin fusion proteins, vectors and host cells comprising an albumin fusion protein nucleic acid, compositions and kits comprising an albumin fusion protein, the method of extending the shelf-life of a therapeutic protein by fusion with albumin, and the treatment of disease using an albumin fusion protein. The albumin fusion proteins may be used in the treatment of metabolic/endocrine disorders, diabetes and diabetes-related conditions. Specifically the albumin fusion proteins may be used to treat type 1 and type 2 diabetes, hyperglycaemia, neural disorders (especially neuropathy), retinopathy, cardiovascular disorders (especially heart disease, renal disorders and obesity. The proteins may also be used in a method of maintaining a basal glucose level in a patient and in a method for losing weight. The present sequence is related to the invention.

L149 ANSWER 55 OF 55 DGENE COPYRIGHT 2004 THOMSON DERWENT on STN
ACCESSION NUMBER: ADH22055 DNA DGENE
TITLE: New albumin fusion protein, useful for preparing a composition for treating diabetes mellitus.
INVENTOR: Rosen C A; Haseltine W A
PATENT ASSIGNEE: (HUMA-N)HUMAN GENOME SCI INC.
PATENT INFO: WO 2003059934 A2 20030724 999p
APPLICATION INFO: WO 2002-US40892 20021223
PRIORITY INFO: US 2001-341811P 20011221
US 2002-350358P 20020124
US 2002-359370P 20020226
US 2002-360000P 20020228
US 2002-367500P 20020327
US 2002-370227P 20020408
US 2002-378950P 20020510
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US 2002-402131P 20020809
US 2002-402708P 20020813
US 2002-411355P 20020918
US 2002-414984P 20021002
US 2002-417611P 20021011
US 2002-420246P 20021023
US 2002-423623P 20021105
DOCUMENT TYPE: Patent
LANGUAGE: English
OTHER SOURCE: 2003-598501 [56]
DESCRIPTION: **Exendin4** codon optimised oligo EXTC-3, SEQ ID NO:852.
AN ADH22055 DNA DGENE
AB The invention relates to fusion proteins comprising human serum albumin (ADH21530) and a therapeutic polypeptide such as a therapeutic protein, antibody or peptide or their variants or fragments. The therapeutic protein may be fused to the N-terminus, the C-terminus or both termini of albumin via a linker. The albumin component of the fusion proteins prolongs the shelf-life and the in vitro and vivo biological activity of the proteins compared with those of the corresponding therapeutic proteins on their own. The invention also relates to nucleic acids encoding albumin fusion proteins, vectors and host cells comprising an albumin fusion protein nucleic acid, compositions and kits comprising an albumin fusion protein, the method of extending the shelf-life of a therapeutic protein by fusion with albumin, and the treatment of disease using an albumin fusion protein. The albumin fusion proteins may be used in the treatment of metabolic/endocrine disorders, diabetes and diabetes-related conditions. Specifically the albumin fusion proteins may be used to treat type 1 and type 2 diabetes, hyperglycaemia, neural disorders (especially neuropathy), retinopathy, cardiovascular disorders (especially heart disease, renal disorders and obesity. The proteins may also be used in a method of maintaining a basal glucose level in a patient and in a method for losing weight. The present sequence is

related to the invention.

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